IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH,	)	
Plaintiff,	)	
	)	Civil Action No.: 06-222 JJF
v.	)	
	)	**PUBLIC VERSION**
IMPAX LABORATORIES, INC.,	)	
Defendant.	)	

DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M. IN SUPPORT OF IMPAX'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF

DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M., IN SUPPORT OF IMPAX'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

I, Bertram Spilker, Ph.D., M.D., declare:

1. I am a physician, pharmacologist, clinical trials and drug development expert and consultant with 40 years of experience in these areas. My qualifications are set forth more fully in paragraphs 1 through 9 of my previous declaration.

"Diminished Incidence of Nausea and Emesis"

2. On page 31 of its brief, Wyeth argues that the word "diminished" can refer to a lessening in degree. It is true that "diminished" can mean a lessening in degree, but "diminished" is an adjective that modifies the noun it precedes. Thus, "diminished nausea" could conceivably mean a lessening in degree of nausea. If the inventors had claimed "diminished nausea and emesis," Wyeth's

construction – a reduction in "degree and/or frequency of nausea and emesis" – could plausibly be correct.

3. However, the patent did not claim "diminished nausea and emesis;" the patent claimed "diminished incidence(s) of nausea and emesis." "Diminished" does not modify "nausea;" it modifies "incidence(s)." Thus, even using Wyeth's definition of "diminished," the proper construction could only read "a lessening in the degree of *incidence* of nausea and emesis." Wyeth's definition of "diminished," therefore, does not provide any information about the definition of "incidence."

4. As I explained in my previous declaration, "incidence" has a clear meaning to one of ordinary skill in the art, referring to a *number or percent* of patients exhibiting a symptom or disease. The word "incidence" is not used to refer to the *severity* of a given symptom. The language of the claim is plain. The claim refers to the *incidence* of nausea and emesis, not the *severity* of the nausea and emesis, that is diminished. If one were to use Wyeth's reading of the claim, the word "incidence" would add nothing to the meaning of the sentence.

5. As I explained in my previous declaration, "incidence" is a term of art. It has a narrower meaning in the art than in ordinary discourse. Thus, it is not surprising that the five medical dictionaries I cited in paragraph 16 of my previous declaration define "incidence" as the number of patients within a population who exhibit a disease or symptom, while the two layman's dictionaries cited in Wyeth's brief define "incidence" in a broader, everyday sense.

6. I have consulted a variety of sources to more comprehensively evaluate how the term "incidence" is used in different medical areas. I have found in all the areas examined that the term "incidence" is used in the more narrow,

restricted definition of the term described in my previous declaration and used by all people who are of ordinary skill in the art. These other areas are described below.

7. Medical dictionaries. My previous declaration presented numerous definitions of "incidence" in standard medical dictionaries.

8. Medical Literature. To better document the actual use of the term "incidence" in the medical literature, I consulted a wide variety of medical literature quoted in the PubMed database at www.pubmed.gov. There, I found many publications which confirmed the use of "incidence" exactly as described above, of which the following are examples:

- Kris, M.G., et al. "Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin." J Clin Oncol 1985 Oct;2(10):1379-84. The title of this study confirms the differing uses of "incidence" and "severity" in the art. Ex. 1.
- Braekken, S.K., et al. "Incidence and frequency of cerebral embolic signals in patients with a similar bileaflet mechanical heart valve." Stroke 1995 Jul;26(7):1225-30. The title of this study confirms the differing uses of "incidence" and "frequency" in the art. Ex. 2.
- McNerney, M.E., and Szeto, H.H. "Prenatal nicotine exposure evokes changes in the incidence and degree of fetal electrocortical activation." J Pharmacol Exp Ther. 1993 Dec;267(3):1460-9. The title of this article confirms the differing uses of "incidence" and "degree" in the art. Ex. 3.

- Levinson, D.F. and Devinsky, O. "Psychiatric adverse events during vigabatrin therapy." Neurology 1999 Oct 22; 53(7):1503-1511. This study sought "to determine the incidence of psychiatric adverse events associated with vigabatrin therapy." The study expressed the resulting incidence as a percentage of individuals in the population who experienced one or more adverse events. Ex. 4.

- Within an hour on this site, I had found numerous additional articles using this definition of "incidence." However, I did not find any article using the word "incidence" to refer to level or severity.

9. FDA. To confirm my understanding of how the term "incidence" is used by the FDA, I contacted Jeff Fritsch, R.Ph., Regulatory Review Officer at the FDA's Office of Orphan Products Development. He stated to me:

> We look at incidence for review purposes as the number of patients diagnosed with a specific disease or condition in a given year.

In order to confirm that this definition is widely used throughout the FDA, I also consulted the FDA's website and found numerous examples which confirmed that the use of "incidence" is identical to that mentioned by Mr. Fritsch and the medical literature. A few of these examples are an FDA letter dated June 8, 1995 (Ex. 5) which uses incidence to describe the number of patients with a condition, and a Guidance for Industry dated February 2007 that refers to the "incidence or severity" of certain epidemics, demonstrating that incidence and severity have different meanings (Ex. 6). I found many other examples located on the FDA website that all supported Impax's construction.

10. Wyeth. Wyeth's package insert for Effexor XR also uses the term "incidence" to refer to the *number or percent* of patients experiencing nausea over a given time period. (Ex. 7.) Table 1 uses "incidence" in its title and refers to the percent of patients experiencing certain side effects while taking Effexor XR. WYETH 006-000122. Table 2 uses "percentage of patients" in the title, and footnote 5 states that "incidence is based on the number of men." WYETH 006-000131. The heading on the next page refers to "Adverse Events Occurring at an Incidence of 2% of More Among Effexor XR-Treated Patients" and the following paragraph uses incidence several times, all again referring to the number or percentage of patients having certain side effects. WYETH 006-000132. Similarly, Tables 3 , 4 and 5 all use "incidence" in the titles and all are referring to the number or percentage of patients that experienced certain side effects. WYETH 006-000133. Footnotes 7 and 9 of Table 3 state explicitly that "incidence is based on the number of [male or female] patients." WYETH 006-000134. It is clear that one of ordinary skill in the art would understand that "incidence" as used in Wyeth's package insert for Effexor XR refers to the number or percentage of patients experiencing a particular event.

11. Tables 3, 4 and 5 list nausea and vomiting (emesis) as adverse events that patients experienced while taking Effexor XR, for instance, Table 3 reports that 31% of patients reported nausea, and 4% of patients reported vomiting (emesis). WYETH 006-000133.

12. Package inserts are constructed at great length and where every word is carefully considered and discussed between FDA and the sponsor. This means that the word "incidence" was not casually used but was felt to be a precise way of expressing the concept of number or percent of patients.

13. In summary, based on the patent specification, as well as my own knowledge and experience, medical dictionaries, the medical literature, the FDA and Wyeth's own documents about Effexor XR, one of ordinary skill in the art would understand the term "incidence" to refer to the number or percent of patients. This definition does not include any reference to either severity or degree.

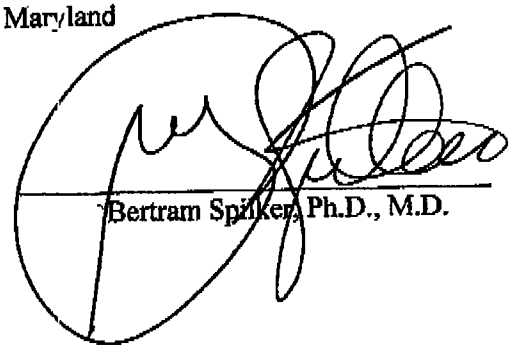
"Therapeutic Metabolism of Plural Daily Doses"

14. I note that none of Wyeth's experts were able to provide a definition for "therapeutic metabolism." This is not surprising, since, as I noted in my previous declaration, I do not believe this term has any commonly accepted meaning to one of ordinary skill in the art.

15. Wyeth's expert, Dr. Sawchuck, did not provide a definition of the term "therapeutic metabolism of plural daily doses." Dr. Sawchuck stated that "therapeutic" means that "the blood levels experienced by a patient treated with an extended release formulation of venlafaxine hydrochloride during a 24 hour period are . . . sufficient to provide relief from the condition being treated over the course of therapy." Sawchuck Decl. at 9. But the claim does not refer to the "therapeutic metabolism" of "an extended release formulation." Instead, the claim refers to "the therapeutic metabolism of plural daily doses," referring to the immediate-release venlafaxine product (requiring more than one daily dose), not Wyeth's extended release product (requiring only a single daily dose).

16. For this reason, Dr. Sawchuck's declaration sheds no light on the term as it is used in the claim.

17. I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that this declaration was executed on this 25th day of May, 2007 at Bethesda, Maryland



Bertram Spilker, Ph.D., M.D.

EXHIBIT 1

Journal of Clinical Oncology, Vol 3, 1379-1384, Copyright © 1985 by American Society of Clinical Oncology

ARTICLES

Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin

MG Kris, RJ Gralla, RA Clark, LB Tyson, JP O'Connell, MS Wertheim and DP Kelsen

Although many trials have evaluated the severity and treatment of nausea and vomiting immediately after cisplatin administration, no studies have focused on vomiting occurring more than 24 hours after chemotherapy--delayed emesis. Two consecutive trials were undertaken to evaluate the incidence, course (trial 1), and severity (trial 2) of delayed nausea and emesis and to develop methods to study these conditions. Eighty-six patients receiving cisplatin (120 mg/m2) for the first time were entered. On the day of cisplatin treatment, all received intravenous (IV) metoclopramide (3 mg/kg X 2 doses) plus dexamethasone (20 mg IV X 1 dose) with either diphenhydramine (50 mg IV) or lorazepam (1.0 to 1.5 mg/m2). Sixty-two percent of patients experienced no vomiting during the 24 hours immediately after administration of cisplatin. Overall, 93% of studied patients experienced some degree of delayed nausea or vomiting from 24 to 120 hours after cisplatin. In trial 1, the incidence of delayed vomiting ranged from 21% to 61% and delayed nausea from 24% to 78% in 58 patients. The highest incidence of both delayed nausea and emesis occurred during the period from 48 to 72 hours after administration of cisplatin. Patients who had no emesis during the initial 24 hours after cisplatin were less likely to experience delayed emesis. The severity of delayed nausea and vomiting was evaluated in 28 patients in trial 2. The amount of delayed nausea and vomiting was assessed daily by patients using a visual analogue scale and by an observer rating. The highest nausea and vomiting scores were seen during the period from 48 to 72 hours after administration of cisplatin, with acceptable correlation between patient scores and observer ratings. Although the nausea and vomiting occurring 24 or more hours after cisplatin administration is not as severe as that seen during the initial 24 hours after administration of cisplatin in patients not receiving antiemetics, it is a common condition that merits both further study and specific treatment.

This article has been cited by other articles: (Search Google Scholar for Other Citing Articles)

Journal of Pediatric Oncology Nursing HOME

D. L. Robinson and B. A. Carr
Delayed Vomiting in Children With Cancer After Receiving Moderately High or Highly Emetogenic Chemotherapy
Journal of Pediatric Oncology Nursing, March 1, 2007; 24(2): 70 - 80.
[Abstract] [PDF]

Annals of Oncology HOME

M. Aapro, S. Grunberg, G. Manikhas, G Olivares, T Suarez, S. Tjulandin, L. Bertoli, F Yunus, B Morrica, F Lordick, and A Macciocchi
A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy
Ann. Onc., September 1, 2006; 17(9): 1441 - 1449.
[Abstract] [Full Text] [PDF]

JOURNAL OF CLINICAL ONCOLOGY HOME

M. G. Kris, P. J. Hesketh, M. R. Somerfield, P. Feyer, R. Clark-Snow, J. M. Koeller, G. R. Morrow, L. W. Chinnery, M. J. Chesney, R. J. Gralla, and S. M. Grunberg
American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006
J. Clin. Oncol., June 20, 2006; 24(18): 2932 - 2947.
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M. G. Kris
Why Do We Need Another Antiemetic? Just Ask.
J. Clin. Oncol., November 15, 2003; 21(22): 4077 - 4080.
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W. C. Mertens, D. J. Higby, D. Brown, R. Parisi, J. Fitzgerald, E. M. Benjamin, and P. K. Lindenauer
Improving the Care of Patients With Regard to Chemotherapy-Induced Nausea and Emesis: The Effect of Feedback to Clinicians on Adherence to Antiemetic Prescribing Guidelines
J. Clin. Oncol., April 1, 2003; 21(7): 1373 - 1378.
[Abstract] [Full Text] [PDF]

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D. Campos, J. R. Pereira, R. R. Reinhardt, C. Carracedo, S. Poli, C. Vogel, J. Martinez-Cedillo, A. Erazo, J. Wittreich, L.-O. Eriksson, A. D. Carides, and B. J. Gertz
Prevention of Cisplatin-Induced Emesis by the Oral Neurokinin-1 Antagonist, MK-869, in Combination With Granisetron and Dexamethasone or With Dexamethasone Alone
J. Clin. Oncol., March 15, 2001; 19(6): 1759 - 1767.
[Abstract] [Full Text] [PDF]

Journal of Oncology Pharmacy Practice HOME

A. Hole, A. Conway, and S. Quadir
Audit of efficacy of 3 mg versus 1 mg of intravenous granisetron as antiemetic prophylaxis against acute emesis caused by cisplatin or melphalan
Journal of Oncology Pharmacy Practice, December 1, 1999; 5(4): 194 - 196.

[Abstract] [PDF]

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R. J. Gralla, D. Osoba, M. G. Kris, P. Kirkbride, P. J. Hesketh, L. W. Chinnery, R. Clark-Snow, D. P. Gill, S. Groshen, S. Grunberg, J. M. Koeller, G. R. Morrow, E. A. Perez, J. H. Silber, and D. G. Pfister

Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines

J. Clin. Oncol., September 1, 1999; 17(9): 2971 - 2971.

[Full Text] [PDF]

The Oncologist HOME

P. J. Hesketh

Defining the Emetogenicity of Cancer Chemotherapy Regimens: Relevance to Clinical Practice

Oncologist, June 1, 1999; 4(3): 191 - 196.

[Abstract] [Full Text]

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R. M. Navari and P. J. Hesketh

Use of Placebos in Delayed-Emesis Studies

J. Clin. Oncol., May 1, 1999; 17(5): 1644 - 1644.

[Full Text] [PDF]

The NEW ENGLAND JOURNAL of MEDICINE HOME

R. M. Navari, R. R. Reinhardt, R. J. Gralla, M. G. Kris, P. J. Hesketh, A. Khojasteh, H. Kindler, T. H. Grote, K. Pendergrass, S. M. Grunberg, A. D. Carides, B. J. Gertz, and The L-754,030 Antiemetic Trials Group

Reduction of Cisplatin-Induced Emesis by a Selective Neurokinin-1-Receptor Antagonist

N. Engl. J. Med., January 21, 1999; 340(3): 190 - 195.

[Abstract] [Full Text] [PDF]

The NEW ENGLAND JOURNAL of MEDICINE HOME

S. M. Grunberg and P. J. Hesketh

Control of Chemotherapy-Induced Emesis

N. Engl. J. Med., December 9, 1993; 329(24): 1790 - 1796.

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H. J. Durivage and N. L. Burnham

Prevention and Management of Toxicities Associated With Antineoplastic Drugs

Journal of Pharmacy Practice, January 1, 1991; 4(1): 27 - 48.

[PDF]

EXHIBIT 2

(*Stroke.* 1995;26:1225-1230.)

Articles

Incidence and Frequency of Cerebral Embolic Signals in Patients With a Similar Bileaflet Mechanical Heart Valve

Presented at the 19th International Joint Conference on Stroke and Cerebral Circulation, San Diego, Calif, February 17-19, 1994.

Sigrun K. Brækken, MD; David Russell, MD, PhD, FRCPE; Rainer Brucher, PhD Jan Svennevig, MD, PhD

From the Departments of Neurology and Surgery, Rikshospitalet, The National Hospital, University of Oslo, Norway; and the Institute of Medical Engineering, FH Ulm, Germany.

Correspondence to S.K. Brækken, MD, Department of Neurology, Rikshospitalet, The National Hospital, Pilestredet 32, N-0027 Oslo, Norway.

Background and Purpose The aim of this study was to determine the incidence and frequency of cerebral embolic signals in a patient population with the same mechanical heart valve using transcranial Doppler examination. Furthermore, it aimed to identify patient and valve characteristics that correlated with the occurrence of these signals.

Methods Ninety-two patients with Carbomedics valves and 15 healthy control subjects took part in the study.

Thirty-six patients were examined before and immediately after valve implantation (group 1), 34 patients 1 year after surgery (group 2), and 22 patients 5 years after surgery (group 3). Cerebral embolic signals were detected using transcranial Doppler monitoring of the right middle cerebral artery.

Results Asymptomatic cerebral embolic signals were detected in 87% of the total 92 patients, in 77.8% of group 1 patients, in 91.2% of group 2 patients, and in 95.5% of group 3 patients. No cerebral embolic signals were detected in group 1 patients before surgery or in control subjects. The incidence (P=.04) and frequency (P=.002) of cerebral embolic signals increased significantly with longer duration of valve implantation. A significant positive correlation was also found between frequency of cerebral embolic signals and valve size (r=.4326, P=.00001). Median frequency of embolic signals in patients with a history suggestive of cerebrovascular events (n=14) was 60 signals per hour compared with 11 signals per hour in those with no such history (n=42; P=.04).

Conclusions The incidence and frequency of cerebral embolic signals increased with the duration of valve implantation. The frequency of these signals also was dependent on valve size. Patients who had experienced cerebrovascular symptoms had a higher frequency of cerebral embolic signals compared with those with no such signals. These results should be interpreted with caution but suggest that this method could be of help in assessing the risk of stroke in prosthetic heart valve patients and that prospective clinical studies should now be carried out.

Key Words: embolism • heart valve prosthesis • ultrasonics

This article has been cited by other articles: (Search Google Scholar for Other Citing Articles)

THE ANNALS OF THORACIC SURGERY HOME

M. Ruel, R. G. Masters, F. D. Rubens, P. J. Bedard, A. L. Pipe, W. G. Goldstein, P. J. Hendry, and T. G. Mesana

Late incidence and determinants of stroke after aortic and mitral valve replacement

Ann. Thorac. Surg., July 1, 2004; 78(1): 77 - 83.

[Abstract] [Full Text] [PDF]

Perfusion HOME

V. Dalinin, P. S. Lingaas, K. Hatteland, and J. L Svennevig

Carotid Doppler microembolic signals in patients one year after heart valve surgery

Perfusion, December 1, 2003; 18(6): 333 - 337.

[Abstract] [PDF]

Stroke HOME

R. Brucher and D. Russell

Automatic Online Embolus Detection and Artifact Rejection With the First Multifrequency Transcranial Doppler

Stroke, August 1, 2002; 33(8): 1969 - 1974.

[Abstract] [Full Text] [PDF]

Stroke HOME

D. Russell and R. Brucher

Online Automatic Discrimination Between Solid and Gaseous Cerebral Microemboli With the First Multifrequency

Transcranial Doppler
Stroke, August 1, 2002; 33(8): 1975 - 1980.
[Abstract] [Full Text] [PDF]

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D. Georgiadis, S. Braun, F. Uhlmann, G. M. Bernacca, W. J. Schulte-Mattler, S. Zierz, and H. R. Zerkowski
Doppler microembolic signals in patients with two different types of bileaflet valves
J. Thorac. Cardiovasc. Surg., June 1, 2001; 121(6): 1101 - 1116.
[Abstract] [Full Text] [PDF]

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C. R. Wilhelm, J. Ristich, L. E. Knepper, R. Holubkov, S. R. Wisniewski, R. L. Kormos, and W. R. Wagner
Measurement of Hemostatic Indexes in Conjunction With Transcranial Doppler Sonography in Patients With Ventricular Assist Devices
Stroke, December 1, 1999; 30(12): 2554 - 2561.
[Abstract] [Full Text] [PDF]

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G. Deklunder, M. Roussel, J.-L. Lecroart, A. Prat, and C. Gautier
Microemboli in Cerebral Circulation and Alteration of Cognitive Abilities in Patients With Mechanical Prosthetic Heart Valves
Stroke, September 1, 1998; 29(9): 1821 - 1826.
[Abstract] [Full Text] [PDF]

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D. Georgiadis, R. W. Baumgartner, R. Karatschai, A. Lindner, and H. R. Zerkowski
Further evidence of gaseous embolic material in patients with artificial heart valves
J. Thorac. Cardiovasc. Surg., April 1, 1998; 115(4): 808 - 810.
[Abstract] [Full Text] [PDF]

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E. Bernd Ringelstein, D. W. Droste, V. L. Babikian, D. H. Evans, D. G. Grosset, M. Kaps, H. S. Markus, D. Russell, and M. Siebler
Consensus on Microembolus Detection by TCD
Stroke, March 1, 1998; 29(3): 725 - 729.
[Abstract] [Full Text] [PDF]

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U. Sliwka and D. Georgiadis
Clinical Correlations of Doppler Microembolic Signals in Patients With Prosthetic Cardiac Valves : Analysis of 580 Cases
Stroke, January 1, 1998; 29(1): 140 - 143.
[Abstract] [Full Text] [PDF]

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D. W. Droste, T. Hansberg, V. Kemeny, D. Hammel, G. Schulte-Altedorneburg, D. G. Nabavi, M. Kaps, H. H. Scheld, and E. B. Ringelstein
Oxygen Inhalation Can Differentiate Gaseous From Nongaseous Microemboli Detected by Transcranial Doppler Ultrasound
Stroke, December 1, 1997; 28(12): 2453 - 2456.

[Abstract] [Full Text]

Stroke HOME

D. Georgiadis, A. Wenzel, D. Lehmann, A. Lindner, H.R. Zerkowski, S. Zierz, and M.P. Spencer

Influence of Oxygen Ventilation on Doppler Microemboli Signals in Patients With Artificial Heart Valves

Stroke, November 1, 1997; 28(11): 2189 - 2194.

[Abstract] [Full Text]

Circulation HOME

A. Notzold, D. W. Droste, G. Hagedorn, S. Berndt, M. Kaps, B. Graf, and H. H. Sievers

Circulating Microemboli in Patients After Aortic Valve Replacement With Pulmonary Autografts and Mechanical Valve Prostheses

Circulation, September 16, 1997; 96(6): 1843 - 1846.

[Abstract] [Full Text]

Stroke HOME

V. L. Babikian, C. A. C. Wijman, C. Hyde, N. L. Cantelmo, M. R. Winter, E. Baker, and V. Pochay

Cerebral Microembolism and Early Recurrent Cerebral or Retinal Ischemic Events

Stroke, July 1, 1997; 28(7): 1314 - 1318.

[Abstract] [Full Text]

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D. Georgiadis, M. Preiss, A. Lindner, Y. Gybels, S. Zierz, and H. R. Zerkowski

Doppler Microembolic Signals in Children With Prosthetic Cardiac Valves

Stroke, July 1, 1997; 28(7): 1328 - 1329.

[Abstract] [Full Text]

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D. Georgiadis, A. Lindner, M. Manz, M. Sonntag, P. Zunker, H. R. Zerkowski, and M. Borggrefe

Intracranial Microembolic Signals in 500 Patients With Potential Cardiac or Carotid Embolic Source and in Normal Controls

Stroke, June 1, 1997; 28(6): 1203 - 1207.

[Abstract] [Full Text]

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H. S. Markus and J. Molloy

Use of a Decibel Threshold in Detecting Doppler Embolic Signals

Stroke, April 1, 1997; 28(4): 692 - 695.

[Abstract] [Full Text]

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D. W. Droste, G. Hagedorn, A. Notzold, H.-J. Siemens, H. H. Sievers, and M. Kaps

Bigated Transcranial Doppler for the Detection of Clinically Silent Circulating Emboli in Normal Persons and Patients With Prosthetic Cardiac Valves

Stroke, March 1, 1997; 28(3): 588 - 592.

[Abstract] [Full Text]

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Clinically Silent Microemboli in Patients With Artificial Prosthetic Aortic Valves Are Predominantly Gaseous and Not Solid
Stroke, February 1, 1997; 28(2): 322 - 325.
[Abstract] [Full Text]

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M. Daffertshofer, S. Ries, U. Schminke, and M. Hennerici
High-Intensity Transient Signals in Patients With Cerebral Ischemia
Stroke, October 1, 1996; 27(10): 1844 - 1849.
[Abstract] [Full Text]

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A.M. Forteza, V.L. Babikian, C. Hyde, M. Winter, and V. Pochay
Effect of Time and Cerebrovascular Symptoms on the Prevalence of Microembolic Signals in Patients With Cervical Carotid Stenosis
Stroke, April 1, 1996; 27(4): 687 - 690.
[Abstract] [Full Text]

EXHIBIT 3

1: J Pharmacol Exp Ther. 1993 Dec;267(3):1460-9.

Links

Prenatal nicotine exposure evokes changes in the incidence and degree of fetal electrocortical activation.

McNerney ME, Szeto HH.

Department of Pharmacology, Cornell University Medical College, New York.

The effects of acute and chronic nicotine (N) administration on fetal electrocorticogram (ECoG) were investigated with spectral analysis. Fetal lambs were instrumented surgically to permit unanesthetized ECoG monitoring and N administration. Acute exposure studies used 4-hr constant-rate infusions at 0.6, 3 or 10 mg/hr. Chronic exposure studies used continuous infusions at 1.2 mg/hr for 7 days. The fast Fourier transform and several derivative parameters were used to quantitate the fetal ECoG during both control records and N infusions. Four states were identified and quantitated in the control ECoG: high-voltage slow activity (State I); low-voltage, fast activity (State IV); and two transitional states of intermediate amplitude and frequency. Acute N infusions elicited changes in the incidence and degree of electrocortical activation that were biphasically dose-related. The 0.6-mg/hr infusion evoked electrocortical activation through an increase in the incidence of State IV. Higher infusion rates elicited progressively less electrocortical activation. The 3-mg/hr infusion affected marginal activation, through a reduction in the incidence of State I. The 10-mg/hr infusion elicited mixed activation and depression, as assessed by multiple parameter changes. Desensitization of several responses diminished the magnitude of depressive effect observed during the 3- and 10-mg/hr infusions. Chronic nicotine infusions elicited progressive augmentation of electrocortical activation, through increases in the incidence and frequencies of State IV. Tolerance to this activating response was not observed.

PMID: 8263808 [PubMed - indexed for MEDLINE]

EXHIBIT 4

Neurology 1999;53:1503

Articles

Psychiatric adverse events during vigabatrin therapy

Douglas F. Levinson, MD and Orrin Devinsky, MD

From the Department of Psychiatry (Dr. Levinson), MCP Hahnemann University, Philadelphia, PA; and the Departments of Neurology, Neurosurgery, and Psychiatry (Dr. Devinsky), New York University School of Medicine, New York, NY.

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Article Abstract

OBJECTIVE: To determine the incidence of psychiatric adverse events associated with vigabatrin therapy, we reviewed data from US and non-US double-blind, placebo-controlled trials of vigabatrin as add-on therapy for treatment-refractory partial epilepsy.

METHODS: "Verbatim" terms from investigators' reports had been translated into standard "preferred" terms using an adverse event dictionary. Terms for psychiatric events were then combined into categories for analysis of rates during vigabatrin versus placebo treatment.

RESULTS: Compared with placebo, vigabatrin subjects had a higher incidence of events coded as depression (12.1% versus 3.5%, $p < 0.001$) and psychosis (2.5% versus 0.3%, $p = 0.028$); there were no significant differences between treatment groups for aggressive reaction, manic symptoms, agitation,

emotional lability, anxiety, or suicide attempt. Although depression and psychosis were typically observed during the first 3 months, most studies were 12 to 18 weeks long, so that definitive conclusions could not be reached about timing of events. Psychosis was generally transient and reported to be responsive to reduction or discontinuation of vigabatrin or to neuroleptic treatment. Depression was typically mild. Serious depression, defined as discontinued from the study, hospitalized, or suicide attempt, or coded as psychotic depression, occurred in only 9 of the 49 vigabatrin-treated patients with depression.

CONCLUSIONS: Vigabatrin use in treatment-refractory partial epilepsy is associated with increased occurrence of depression and of psychosis, although the frequency of psychosis is apparently lower than previously reported. Clinical experience suggests that these adverse events respond to reduction of vigabatrin dose or to counteractive psychotropic treatment.

Key words: Vigabatrin—Psychiatric adverse events—Antiepileptic drugs—Psychosis—Depression.

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Concern about psychiatric adverse events (AEs) during vigabatrin (VGB) therapy was generated primarily by several small series of reports in the neurologic literature.[1-5] These reports described uncontrolled observations of patients with treatment-resistant partial complex epilepsy who developed acute psychotic symptoms (such as delusions or hallucinations) during VGB therapy. To determine the frequency of the types of psychiatric events reported in these uncontrolled observations, we examined data from controlled trials of VGB conducted by the sponsor of the antiepileptic drug, Hoechst Marion Roussel, Inc. (HMR). A method was developed to compare treatment-emergent behavioral events in patients from all randomized, double-blind studies in which VGB or placebo was added to previous antiepileptic regimens in patients with treatment-resistant partial epilepsy.

Interpretation of psychiatric AE data is complicated by several factors. VGB has been studied almost exclusively as add-on therapy for patients with treatment-resistant partial seizures. These patients have a high incidence of neuropsychiatric symptoms, including psychosis,[6] presumably due to paroxysmal and persistent neuronal dysfunction or lesions in limbic areas as well as to unremitting electrical activity and treatment with multiple drugs that also have potential neuropsychiatric effects. Psychosis has been associated with decreases[5] and increases[7] in seizure frequency. Depression has also been linked to seizures disorders and can develop during withdrawal from antiepileptic drugs[8] or with the use of certain antiepileptic drugs (e.g., barbiturates). The high frequency of psychiatric symptoms in these patients complicates the screening process to exclude subjects with any history of such symptoms from clinical trials. Thus, although all trials had exclusion criteria for clinically significant psychiatric disorder, some patients with psychiatric histories were admitted. Because these factors confound the assessment of neuropsychiatric events in the epilepsy population, the present analysis was undertaken to help clarify the role of VGB as a cause of behavioral disorders by evaluating data generated only from double-blind, placebo-controlled studies.

Another issue in evaluating these data is that, as in other clinical trials of antiepileptic agents, VGB trials were not designed specifically to study psychiatric syndromes. Most available safety data are AE reports from epilepsy center neurologists (with psychiatric consultation only when medically indicated). The frequency of clinically significant psychiatric syndromes cannot be determined with certainty from this type of data. Recognizing this limitation of the available data, we attempted to estimate the frequency of psychiatric syndromes by grouping clinically related terms in the AEs dictionary to provide maximum estimates, as described below.

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Selection of studies. Two HMR databases were used in these analyses. The first included subjects from all "primary" US and non-US double-blind clinical trials of VGB versus placebo as add-on therapy in adult patients for treatment-refractory partial epilepsy for which case report forms were available for documentation and consistent coding of AEs. The second database included, in addition to these subjects, those from all other US and non-US HMR-sponsored controlled or uncontrolled clinical studies in both epilepsy and nonepilepsy adult patients (primary plus secondary studies).

For the main analyses discussed below (tables 1 and 2), we considered only the first database—US and non-US primary (double-blind, placebo-controlled) add-on trials. Table 3 lists the studies selected for analysis. Three were true double-blind, placebo-controlled, parallel-group studies: two US trials[9,10] and one Canadian trial (71754-3-C-021). One United Kingdom trial (097/W/UK/04) was a parallel-group study in which all subjects eventually received VGB; in the current analysis, VGB and placebo were compared during the initial 18-week randomization period, before the placebo subjects received VGB, to avoid carryover effects. The six other trials were double-blind, placebo-controlled, crossover studies. Again, only the initial treatment period was included in the present analysis (i.e., patients exposed to VGB during the first randomization period versus those exposed initially to placebo). A total of 717 subjects were included in the analysis of controlled trials (406 treated with VGB, 311 with placebo), with treatment periods ranging from 7 to 18 weeks (most were 12 weeks or longer). All subjects in this analysis were adults with treatment-resistant partial complex epilepsy, with or without secondary generalized seizures.

View this table: [in this window] [in a new window] Table 1. Occurrence of psychiatric combined terms in US and primary non-US placebo-controlled epilepsy trials

View this table: [in this window] [in a new window] Table 3. US and primary non-US placebo-controlled vigabatrin studies

View this table: [in this window] [in a new window] Table 2. Occurrence of "serious" events in patients reporting depression in US and primary non-US placebo-controlled vigabatrin (VGB) epilepsy trials

The data presented in tables 4 and 5 are from the second database (all VGB-treated subjects from all US and non-US trials). Table 4 considers only subjects with preexisting neuropsychiatric disorders drawn from 18 small, uncontrolled, mostly non-US studies that specifically considered such subjects (because they would be excluded from epilepsy trials). None of these studies have been published, and their designs varied considerably. Because patients with a known history of neuropsychiatric disorder were excluded from VGB epilepsy protocols, these studies provide the only data for evaluation of psychiatric AEs in such patients. Table 5 considers all subjects in the primary plus secondary database. Note that this database is drawn from more than 50 trials, so that no complete listing will be attempted here.

View this table: [in this window] [in a new window] Table 4. Occurrence of psychiatric combined terms in uncontrolled US and non-US trials of vigabatrin in subjects with preexisting neuropsychiatric disorders

View this table: [in this window] [in a new window] Table 5. Occurrence of psychiatric combined terms in subjects from all US and non-US vigabatrin (VGB) trials

Coding of AE terms for analysis. AEs had been coded by safety staff at HMR following standard clinical trial procedure, i.e., a dictionary of safety terms was used to map the "verbatim" terms used in investigator reports to "preferred terms" for reporting of safety data. The original coding of non-US trials was completed by regional safety departments in various countries, and during the 18-year period of these VGB investigations several different dictionaries had been used. The Food and Drug Administration requested a safety amendment to the new drug application for VGB with consistent coding. Therefore, HMR's US safety staff re-coded all AEs (not only psychiatric events) for all non-US subjects using the dictionary of safety terms that had been used for US subjects. For consistency, these re-coded data have been used here for all non-US studies. Note, for example, that depression had been noted to be much more frequent in US subjects before the re-coding, but in the re-coded data this difference disappeared, suggesting that the codings are now much more consistent.

Safety data are typically reported as the incidence of each preferred term. However, clinically similar events can be mapped to different terms depending on the exact wording of the original report. To provide a more realistic estimate of related psychiatric events, we grouped the preferred terms into "combined terms" as shown in table 6. Thus, a subject with any event coded as "hallucination,"

"paranoid reaction," "psychosis," or "schizophrenic reaction" or any combination of these terms was counted as having had "psychosis" in the present analysis. The combined terms represent only approximations of the psychiatric syndromes usually denoted by such terms as depression, anxiety, or mania because they are based purely on investigators' reports and not on formal psychiatric assessment. An attempt was made initially to "re-diagnose" psychiatric syndromes based on available coded and narrative information, but results of preliminary analyses were almost identical to those using the combined terms. We therefore decided to rely on analyses of combined terms under the assumption that investigators had access to additional clinical information when reporting these events and that the systematic coding of these reports provides the most valid available information.

View this table: Table 6. Grouping of preferred terms into combined psychiatric event terms
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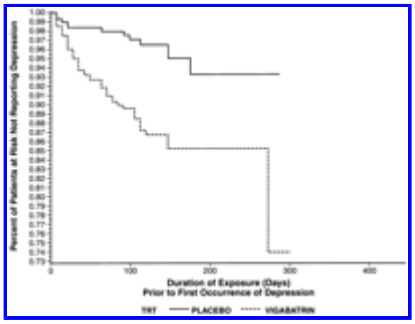
Note that the use of these combined terms results in higher total incidences than would be observed with any one preferred term. For example, the incidence of the preferred term *depression* would be lower than our combined term "depression," which includes several other preferred terms. Thus these data cannot be directly compared with rates of individual psychiatric AEs in package insert data based on individual preferred terms.

Statistical analysis. For each combined term, Fisher's exact test was performed to compare the rates of the event in VGB and placebo subjects, and a two-tailed *p* value was computed. For the main analysis shown in table 1, odds ratios and their 95% confidence intervals were also calculated except where there were no events in the placebo group. Although a more complex analysis could have been justified, the analyses of psychosis and depression represented tests of prior hypotheses. Therefore, correction for multiple testing was not indicated. Tests of the other terms were exploratory in nature.

Timing of events. For events that occurred more frequently in VGB than in placebo subjects, Kaplan-Meier plots (figures 1 and 2) were constructed to illustrate the time pattern in each subject group. For each week, the y-axis values represent the proportion of subjects in each group not yet experiencing the event among the total number of subjects still under study in that group (i.e., excluding dropouts for other reasons and those who had completed the study at that point). Thus, sample size decreased considerably beyond 12 weeks. The variability in duration of studies and the declining sample size over time complicated statistical analysis of timing patterns; therefore, the graphs are presented for descriptive purposes only.

Figure 1. Timing of reported onset of depression (combined term) in vigabatrin (VGB)-treated patients in controlled trials. Shown is a Kaplan-Meier plot of the proportion of patients not yet reported to have experienced depression (combined term, see table 6) by the study day (x-axis), for VGB-treated



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patients in the controlled trials listed in table 3 (considering only the first treatment period in crossover studies). Note that sample size decreases markedly after week 12 (day 84).

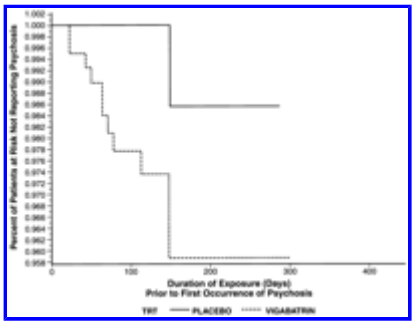

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Figure 2. Timing of reported onset of psychosis (combined term) in vigabatrin-treated patients in controlled trials. As for figure 1, but for proportion of patients not yet reported to have experienced psychosis (combined term).

Other analyses. Several additional analyses were carried out. First, the combined terms were organized into a hierarchy of approximate severity (e.g., psychosis, then aggressive reaction, then manic symptoms, then depression, etc.), and the VGB versus placebo comparisons were repeated for rates of each event in the absence of any of the "higher" events. Results (not shown) were essentially identical to the non-hierarchical analysis. Second, a set of "serious" events was defined (see table 2) for cases of depression, and rates of these outcomes were compared for VGB versus placebo subjects. Third, the rates of each combined term were determined in uncontrolled studies of VGB treatment in other neuropsychiatric disorders (tardive dyskinesia, schizophrenia, or Huntington's disease) (see table 4). The purpose of this descriptive analysis was to determine whether there was any evidence for markedly increased risk of these events in subjects with a history of neuropsychiatric disorder. Fourth, the rates of psychiatric events, grouped by the combined terms as described above, were determined for all patients assigned to VGB in clinical trials, including trials not included in the main analyses (see table 5). This table includes *all* VGB-treated subjects (including those in controlled studies who are also included in tables 1 and 2) in HMR's safety database, using the consistent coding system described above. Data from this much larger sample are presented to determine whether rates of psychiatric AEs in subjects in controlled trials were similar to those in other types of trials. Finally, case narratives of all patients with

behavioral AEs were reviewed.

Analysis of epilepsy subjects with and without psychiatric history was not performed. Each of these epilepsy trials included some exclusion criterion for history. When subjects developed psychiatric symptoms, additional history of events was often obtained. Therefore, comparable information about psychiatric history is not available for subjects with and without a psychiatric event during the trials.

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Comparison of VGB- and placebo-treated subjects. Results of the primary analysis are summarized in table 1. Statistically significant differences between the two groups were found for two of the combined terms: depression ($p < 0.001$) and psychosis ($p = 0.028$). All other types of events were equally common in subjects treated with placebo and with VGB, suggesting that there is no generalized increase in "psychiatric" AEs, but only in depression and psychosis. Odds ratios are also shown. Note the wide 95% confidence interval for the estimated odds ratio for psychosis, suggesting that a larger sample size would be needed to make an accurate estimate.

The number of patients experiencing depression was sufficiently large to consider group differences in serious events (dropped from study, hospitalized, suicide attempt, or psychotic depression), as summarized in table 2. VGB-treated patients had more serious events when considering all these events combined ($p < 0.001$). Even in most cases with serious outcomes, however, depression was not considered sufficiently severe to warrant discontinuing the patient from the study. Only 1.5% of VGB-treated patients (6/406 total patients and 9/49 experiencing depression) and no placebo-treated patients (0/311 total patients and 0/11 experiencing depression) were discontinued due to depression.

Psychiatric AEs in subjects with neuropsychiatric disorders. Table 4 summarizes the frequency of each combined term in uncontrolled VGB trials in patients with neuropsychiatric disorders. The most common events were agitation or aggression, or both. Patients with schizophrenia (including those with tardive dyskinesia, most of whom also had schizophrenia) had exacerbations of psychosis in 5 to 6% of cases; however, note that neuroleptic treatment was discontinued before starting VGB in some of these trials. Depression was not observed more frequently in patients with neuropsychiatric disorders than it was in patients with epilepsy (although methodologies of these studies are not entirely comparable).

Timing of psychosis and depression. Figures 1 and 2 illustrate the timing of onset of psychosis and depression in VGB- and placebo-treated subjects from the controlled trials listed in table 3 and summarized in tables 1 and 2. The data are presented as survival curves, i.e., the proportion of patients who had not yet experienced the event of interest by each study day. These data may be of interest to clinicians. They demonstrate that onsets of both psychosis and of depression occurred at various times during the study treatment periods, so that no main period of risk could be identified. Note that there were few subjects available for analysis beyond 12 weeks because most studies were limited to 12 weeks or less.

Rates of psychiatric AEs in all VGB-treated patients in VGB trials. Table 5 summarizes the rates of psychiatric combined terms in all patients listed in HMR's safety database from all US and non-US controlled and uncontrolled VGB clinical trials. Thus this table includes all subjects for whom data have been shown in tables 1, 2, and 4 as well as all other subjects in HMR-sponsored trials regardless of design. In all but the last column, AEs have been counted only if they occurred during a period of treatment with VGB. Note that for crossover studies, VGB treatment periods are included here regardless of order, whereas in tables 1 and 2 only the first treatment period (VGB or placebo) is considered to avoid carryover effects. For epilepsy subjects, results for each database (US controlled trials, non-US controlled trials, and non-US controlled and uncontrolled trials) are shown separately. The "All" column adds all other patients assigned to a VGB treatment condition in these trials (e.g., patients who only received placebo before removal; patients observed only during a baseline, nontreatment, or washout period; and active controls) and includes events observed in VGB and non-VGB treatment periods. Note that the total incidence of events in the total VGB column is similar to that observed in controlled trials (see table 1), so that the latter subjects appear to be reasonably representative.

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Data from placebo-controlled trials suggest that patients with treatment-resistant partial epilepsy who receive VGB as add-on therapy for 12 to 18 weeks have a small but statistically significant increased risk of developing psychotic symptoms (2.5% versus 0.3% for control subjects) as well as an increased risk of developing some degree of depression (12.1% versus 3.5% for controls). Differences between placebo and VGB treatment groups are not seen for other psychiatric AEs.

Psychosis. Why VGB is associated with an increase in psychotic symptoms in these patients is unknown. Thomas et al.[5] suggested that abrupt cessation of seizures can precipitate psychosis in some patients (i.e., "forced normalization" or "reciprocal psychosis" hypothesis); thereby, drugs that produce remission in some proportion of chronic epilepsy patients might be associated with such a risk. However, no direct evidence from VGB clinical trials supports this explanation for most cases of treatment-emergent psychotic symptoms.

Another potential explanation is the acute increase in dopamine (DA) metabolites in CSF[11] found after administration of VGB. The effects of GABA on dopaminergic neurotransmission is complex, however, and varies from region to region; in addition, no chronic effect of VGB on DA transmission was observed. Ring et al.[12] demonstrated decreased DA-DA_2 receptor binding detected by SPECT during VGB therapy, suggesting alterations in DA activity. Given the low frequency of exacerbations of psychosis in schizophrenia patients treated with VGB, a simple biochemical relationship between VGB and psychosis is unlikely. In the US dose-ranging study,[10] the highest VGB dose (6 g/d) was associated with increased CNS adverse effects, but not specifically with increased hallucinations or delusions.

The case narratives demonstrate that psychotic symptoms were typically mild and transient, with good

response to neuroleptic treatment. Of the 10 patients with psychosis in the VGB group, 4 had a history of similar symptoms, and 1 appeared to have new-onset chronic schizophrenia judged by a consulting psychiatrist to be independent of VGB treatment. Valid assessment of the predictive value of psychiatric history could not be performed on the data collected in these trials.

In most but not all cases of psychotic symptoms during clinical trials, VGB was discontinued as a result. In some cases, VGB was continued, and mild psychotic symptoms such as paranoia resolved spontaneously. In other cases, concurrent neuroleptic medication was successfully administered because, in the physician's judgment, VGB was effective in reducing seizure frequency.[13] An additional report also indicates counteractive neuroleptic medication is effective for treatment-emergent psychotic symptoms in patients receiving VGB therapy.[14]

No evidence is available to determine the risk of psychotic symptoms in patients with other types of epilepsy or with VGB monotherapy. In addition, further data are need to determine whether the neuropsychiatric events are dose sensitive.

Depression. γ-Aminobutyric acid (GABA) may play a role in the pathogenesis and treatment of depression. Current evidence suggests that antidepressant drug activity may be associated with increased GABA-B and decreased GABA-A receptor activity[15] and that there may be inter-individual differences in GABA-A sensitivity in animal models of depression.[16] Thus, GABAergic drugs could have both antidepressant and depressogenic activity. VGB is associated with decreased serotonergic metabolites in CSF,[11] presumably as a direct result of inhibition by GABAergic activity, which would be expected to increase the risk for depression. Depression was a dose-dependent effect observed in the US multiple-dose trials,[10] supporting the hypothesis of a direct neurochemical effect.

In the trials we reviewed, however, depression was usually coded primarily based on emergence of depressed mood. A full depressive syndrome was not observed in most cases (although this could not be assessed completely). Also, depression was sufficiently mild that it resulted in discontinuation of study drug in only 6 of 406 (1.5%) of VGB-treated cases. There are no data to evaluate the risk of depression in patients with other types of epilepsy or with VGB monotherapy, and the predictive value of history of depression is not known. Although clinical experience suggests that antidepressant drug treatment can effectively treat depression in patients undergoing VGB therapy for epilepsy, no controlled studies are available.

Comparison with other antiepileptic drugs. Antiepileptic drugs often have psychotropic effects, and psychiatric AEs, including depression, aggression, and psychosis, have been reported during treatment with carbamazepine[17-19] and sodium valproate.[20] The product labeling for gabapentin (Neurontin package insert, 1998) reports "thinking abnormal" in 1.7% of gabapentin-treated patients in clinical trials compared with 1.3% of placebo-treated patients. It is unclear whether this coding referred to psychotic symptoms or confusion. Depression (as a single preferred term) was reported in only 1.8% of gabapentin-treated patients, but there was a suggestion of a dose effect. Depression was observed in none of the patients receiving 500 mg/d of gabapentin, 1.3 to 1.4% receiving 900 to 1,200 mg/d, and 5.6% receiving 1,800 mg/d. There is some evidence that gabapentin dosages of 1,800 mg/d or more are

required in refractory partial epilepsy patients.[21] Data from clinical trials with other new antiepileptic drugs have apparently not been analyzed by combining related AE terms as described here.

Direct, double-blind parallel-group study of VGB and equally efficacious dosages of other new antiepileptic drugs would be useful to determine whether differences in the risk of psychotic or depressive symptoms exists among the drugs. Three open-label parallel-group studies have been reported briefly in published abstracts, but without details on specific AEs.[22-24] Marson et al.[25] systematically reviewed published and unpublished randomized controlled trials that provided consistent information on efficacy and safety. They identified 20 studies with 3,883 patients who were treated with one of six drugs. The odds ratios (95% confidence intervals) for withdrawal from a study because of toxicity were as follows: gabapentin (1.36 [0.75 to 2.49]), lamotrigine (1.19 [0.79 to 1.79]), tiagabine (1.81 [1.21 to 2.70]), topirimate (2.42 [1.43 to 4.11]), VGB (2.58 [1.26 to 5.27]), and zonisamide (5.70 [1.76 to 18.49]). Overall, they found no statistically significant differences in the effectiveness or toxicity of the six drugs. There was no analysis of specific AEs as causes of subject withdrawal.

AE data for other newer antiepileptic drugs have not been subjected to the kind of analysis presented here, with comparison or patients treated with the study drug versus placebo or comparison drugs in blind parallel-group trials using clinically relevant combined terms that provide a realistic estimate of the incidence of psychiatric AEs. Therefore it is unknown whether other drugs are also associated with increased risk of depression or psychosis in treatment-refractory partial epilepsy patients at clinically effective dosages.

Clinical implications. The risks of psychiatric AEs associated with VGB therapy are modest in relation to the efficacy of VGB. In the trials summarized above, approximately one-half the treatment-refractory patients experienced at least a 50% reduction in seizures, and complete remissions occurred in some cases.[9,10,22] Although reports of treatment-emergent psychosis have received considerable attention, depressed mood was the most common psychiatric AE reported. Depression was typically mild and seldom (1.5%) led to drug discontinuation or other serious outcomes. VGB significantly increased the risk of psychosis, but to a more modest degree than suggested by anecdotal reports: 2.5% of 406 patients in randomized, double-blind trials experienced psychotic symptoms in contrast with more than 10% reported anecdotally by Ring et al.[12] Although clinical investigators may have under-reported psychosis or failed to detect this disorder because no standardized evaluations were employed systematically, we suspect that overt, acute psychotic symptoms of the type reported by Ring et al. were likely to have been observed by clinical trials investigators. The high frequency of depressive symptoms reported in these trials also suggests vigilance in noting behavioral events.

The 2.5% risk of psychotic symptoms in VGB-treated patients in controlled trials was significantly higher than it was in controls, but symptoms were often mild and transient. Of the five VGB-treated patients who experienced apparently treatment-related psychotic symptoms with no history of psychosis, duration of the event was 3, 11, 19, 24, and 60 days. The transient and treatment-responsive nature of the observed psychotic symptoms suggests that, with proper monitoring and early intervention, risk to patients is modest in relation to the efficacy of the drug in severe partial epilepsy. Although most such

events occurred in the first 8 to 12 weeks of therapy, controlled data are not available for treatment periods of longer than 18 weeks; therefore, the duration of the period of increased risk is unknown.

Although some patients with treatment-emergent psychosis had histories of similar symptoms, most patients with preexisting schizophrenia in open-label VGB trials did not experience exacerbations of psychosis. Thus, it is not known whether a history of psychosis predicts an increased risk of treatment-emergent psychosis, and patients with a history of psychosis should not be denied VGB therapy if clinically indicated.

Published studies of VGB as monotherapy for epilepsy confirm that neither depression nor psychosis are frequent clinical problems. Specific AEs were discussed in reports of three open monotherapy trials. Kaelviaeinen et al.[26] reported that 0 of 43 VGB patients were withdrawn for AEs; depression was reported as an AE in 1 subject and psychosis in none. de Feo et al.[27] reported that 2 of 50 patients withdrew for nonpsychiatric AEs; no psychiatric AEs were reported. Tanganelli and Regesta[28] reported that 0 of 26 VGB patients were withdrawn; there were no reports of depression or psychosis. Thus, of the 126 monotherapy patients in these trials, depression was reported in 1 patient and psychosis in none.

Recent reports document the association of visual field defects (VFD) with the use of VGB.[29-33] Clinically significant symptomatic or asymptomatic visual field constriction can develop as well as abnormalities on the electroretinogram. The presumed mechanism is impairment of the highly GABAergic retinal amacrine cells. Based on data from 136 cases (data on file, HMR), approximately 25% of patients on VGB will develop a VFD. There is a potential association between gender and occurrence of VFD, with a slightly higher incidence being reported in men. No association of VFD with age, duration of VGB use, cumulative dose of VGB, duration of epilepsy, or weight or body mass index has been found. A full discussion of this nonpsychiatric AE is beyond the scope of the present paper.

In individual epilepsy cases, it may be difficult to determine whether psychotic symptoms are due to preexisting illness, changes in seizure severity or frequency (e.g., postictal psychosis), or effects of drug therapy. Based on clinical experience and review of these cases, we suggest that when psychotic symptoms develop during VGB therapy, VGB should generally be discontinued, whenever possible, by tapering rather than abrupt discontinuation. If psychotic symptoms are severe or fail to respond rapidly to dose reduction or discontinuation of VGB, neuroleptic treatment may be useful until symptoms resolve. In some cases, a neuroleptic drug has been added when both mild psychotic symptoms and substantial reductions in seizure frequency were observed during VGB therapy, with apparently successful results. However, no controlled data are available comparing potential treatments of psychosis during VGB therapy.

Depression was more frequently associated with VGB therapy than psychosis. It is not known whether a past episode of depression increases the risk, but a careful assessment of history may assist in identifying the earliest signs of treatment-emergent depression. Clinical experience suggests that antidepressant drug therapy can sometimes be added successfully when both depression and substantial reduction of seizure frequency are observed during VGB therapy; but, again, no controlled data are available.

Acknowledgments

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Table 1. Occurrence of psychiatric combined terms in US and primary non-US placebo-controlled epilepsy trials

	Percent of patients with at least one event									
	Parallel controlled				1st period crossover					
	US (024/025)		Primary non-US (021)		Primary non-US		Total			
Combined term	Placebo, n = 135, n (%)	VGB, n = 222, n (%)	Placebo, n = 53, n (%)	VGB, n = 58, n (%)	Placebo, n = 123, n (%)	VGB, n = 126, n (%)	Placebo, n = 311, n (%)	VGB, n = 406, n (%)	*p* Value	Odds ratio (95% CI)
Psychosis	0 (0.0)	5 (2.3)	0 (0.0)	3 (5.2)	1 (0.8)	2 (1.6)	1 (0.3)	10 (2.5)	0.028	7.8 (1.0–61.5)
Aggressive reaction	1 (0.7)	1 (0.5)	1 (1.9)	5 (8.6)	3 (2.4)	6 (4.8)	5 (1.6)	12 (3.0)	0.324	1.9 (0.6–5.4)
Manic symptoms	0 (0.0)	2 (0.9)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	4 (1.0)	0.137	—
Depression	5 (3.7)	28 (12.6)	3 (5.7)	12 (20.7)	3 (2.4)	9 (7.1)	11 (3.5)	49 (12.1)	<0.001	3.7 (1.9–7.3)
Agitation	14 (10.4)	28 (12.6)	5 (9.4)	7 (12.1)	6 (4.9)	9 (7.1)	25 (8.0)	44 (10.8)	0.250	1.4 (0.8–2.3)
Emotional lability	4 (3.0)	11 (5.0)	2 (3.8)	4 (6.9)	3 (2.4)	4 (3.2)	9 (2.9)	19 (4.7)	0.248	1.6 (0.7–3.7)
Anxiety	9 (6.7)	15 (6.8)	6 (11.3)	10 (17.2)	6 (4.9)	13 (10.3)	21 (6.8)	38 (9.4)	0.220	1.4 (0.8–2.5)
Suicide attempt	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	4 (1.0)	0.137	—

VGB = vigabatrin.

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Table 2. Occurrence of "serious" events in patients reporting depression in US and primary non-US placebo-controlled vigabatrin (VGB) epilepsy trials

	Percent of patients with at least one event								
	Parallel controlled				1st period crossover				
	US (024/025)		Primary non-US (021)		Primary non-US		Total		
Serious outcome	Placebo, n = 135, n (%)	VGB, n = 222, n (%)	Placebo, n = 53, n (%)	VGB, n = 58, n (%)	Placebo, n = 123, n (%)	VGB, n = 126, n (%)	Placebo, n = 311, n (%)	VGB, n = 406, n (%)	*p* Value
All depression	5 (3.7)	28 (12.6)	3 (5.7)	12 (20.7)	3 (2.4)	9 (7.1)	11 (3.5)	49 (12.1)	<0.001
"Serious" events:									
Dropped because of depression	0 (0.0)	2 (0.9)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.6)	0 (0.0)	6 (1.5)	0.039
Hospitalization because of depression	0 (0.0)	2 (0.9)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	3 (0.7)	0.262
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Psychotic depression	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0.508
Total serious events	0 (0.0)	5 (2.3)	0 (0.0)	2 (3.4)	0 (0.0)	2 (2.4)	0 (0.0)	9 (2.2)	<0.001

Patients reporting worsening of depression or psychotic depression are included with patients reporting depression. A patient may have more than one serious outcome; therefore, patient totals may not equal the sum of the patient counts for the individual events.

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Table 3. US and primary non-US placebo-controlled vigabatrin studies

Protocol	Study design	Dose, g/d	Duration of first period drug treatment, wk	No. of patients in controlled portion of study (P/V)
71754-3-C-024 (9)	DBPC, parallel	3	16	182 (90/92)
71754-3-C-025 (10)	DBPC, parallel	1, 3, 6	18	174 (45/129)
71754-3-C-021	DBPC, parallel	1–4	12	111 (53/58)
097/W/UK/04	DBPC, parallel, all patients received vigabatrin	2, 3	18	45 (23/22)
097-444	DBPC, crossover	2, 3	12	24 (12/12)
097/W/AUS/01 (34)	DBPC, crossover	2, or 3	8	97 (45/49, 3 baseline drops)
097-247	DBPC, crossover	3	12	16 (9/7)
097-259	DBPC, crossover	2–3	12	31 (16/15)
097-262	DBPC, crossover	1–2	10	11 (4/7)
097-263	DBPC, crossover	1.5, 2, or 3	7	28 (14/14)

(P/V) = placebo/vigabatrin; DBPC = double-blind, placebo-controlled.

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Table 4. Occurrence of psychiatric combined terms in uncontrolled US and non-US trials of vigabatrin in subjects with preexisting neuropsychiatric disorders

Term	Tardive dyskinesia, n = 77, n (%)	Schizophrenia, n = 38, n (%)	Huntington's disease, n = 22, n (%)	Total, n = 137, n (%)
Psychosis	5 (6.5)	2 (5.3)	0 (0.0)	7 (5.1)
Aggressive reaction	9 (11.7)	4 (10.5)	3 (13.6)	16 (11.7)
Manic symptoms	4 (5.2)	2 (5.3)	1 (4.5)	7 (5.1)
Depression	3 (3.9)	3 (7.9)	4 (18.2)	10 (7.3)
Agitation	7 (9.1)	4 (10.5)	2 (9.1)	13 (9.5)
Emotional lability	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.7)
Anxiety	6 (7.8)	3 (7.9)	1 (4.5)	10 (7.3)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 5. Occurrence of psychiatric combined terms in subjects from all US and non-US vigabatrin (VGB) trials

	Epilepsy (VGB treatment periods only)				Total epilepsy + nonepilepsy	
Combined term	US, n = 443, n (%)	Non-US primary, n = 765, n (%)	Non-US primary and secondary, n = 1,499, n (%)	Total, n = 1,942, n (%)	During VGB treatment*, n = 2,515, n (%)	All treatment periods*, n = 2,686, n (%)
Psychosis	19 (4.3)	14 (1.8)	34 (2.3)	53 (2.7)	63 (2.5)	69 (2.6)
Aggressive reaction	4 (0.9)	34 (4.4)	77 (5.1)	81 (4.2)	100 (4.0)	117 (4.4)
Manic symptoms	7 (1.6)	7 (0.9)	11 (0.7)	18 (0.9)	35 (1.4)	45 (1.7)
Depression	65 (14.7)	58 (7.6)	103 (6.9)	168 (8.7)	184 (7.3)	227 (8.5)
Agitation	70 (15.8)	52 (6.8)	122 (8.1)	192 (9.9)	213 (8.5)	251 (9.3)
Emotional lability	41 (9.3)	18 (2.4)	31 (2.1)	72 (3.7)	76 (3.0)	89 (3.3)
Anxiety	67 (15.1)	35 (4.6)	82 (5.5)	149 (7.7)	170 (6.8)	204 (7.6)
Suicide attempt	4 (0.9)	2 (0.3)	5 (0.3)	9 (0.5)	9 (0.4)	10 (0.4)

* The VGB column includes events reported during VGB treatment periods. The All column includes events reported in subjects assigned to VGB treatment during all periods, including VGB or placebo treatment, at baseline and during washout and active control treatment periods.

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Table 6. Grouping of preferred terms into combined psychiatric event terms

Combined term	Preferred terms
Psychosis	Hallucination, paranoid reaction, psychosis, schizophrenic reaction
Depression	Depression, depression psychotic, depression worsened
Agitation	Agitation
Aggressive reaction	Aggressive reaction
Manic symptoms	Manic reaction, euphoria, libido increased, cyclothymic reaction
Suicide attempt	Suicide attempt
Emotional lability	Emotional lability
Anxiety	Anxiety, nervousness

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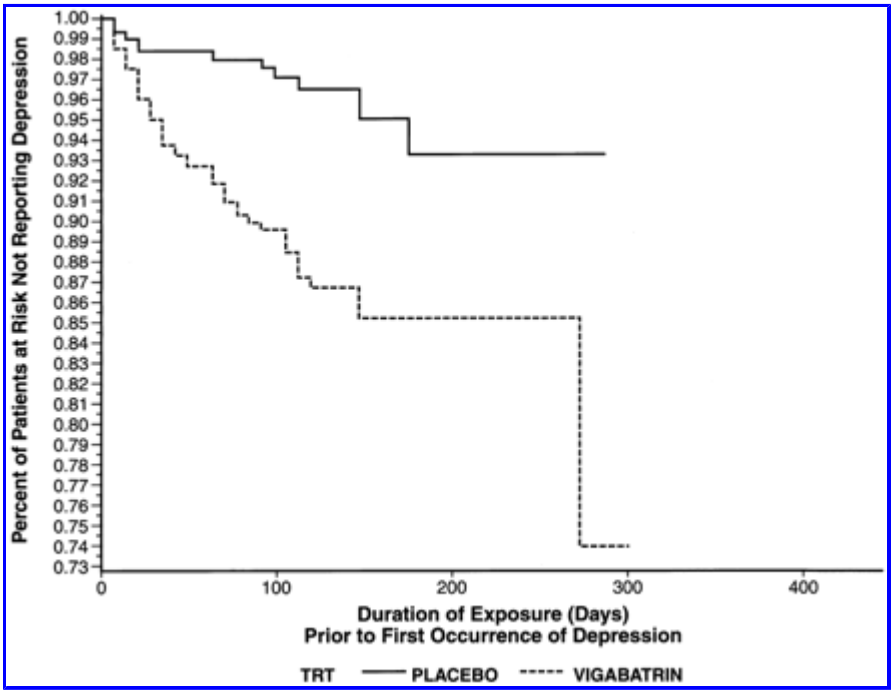

Figure 1. Timing of reported onset of depression (combined term) in vigabatrin (VGB)-treated patients in controlled trials. Shown is a Kaplan-Meier plot of the proportion of patients not yet reported to have experienced depression (combined term, see table 6) by the study day (x-axis), for VGB-treated patients in the controlled trials listed in table 3 (considering only the first treatment period in crossover studies). Note that sample size decreases markedly after week 12 (day 84).

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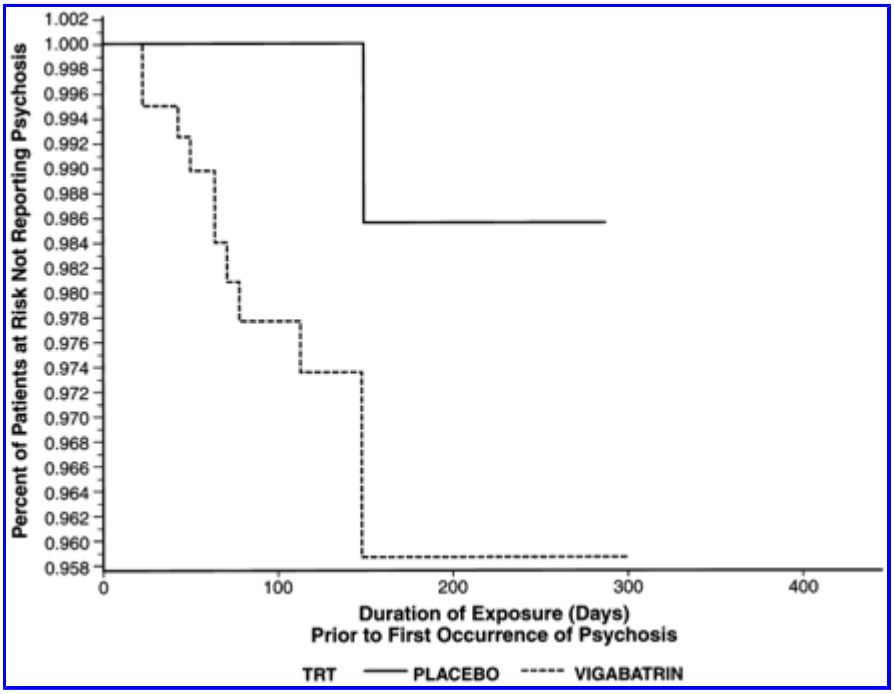

Figure 2. Timing of reported onset of psychosis (combined term) in vigabatrin-treated patients in controlled trials. As for figure 1, but for proportion of patients not yet reported to have experienced psychosis (combined term).

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EXHIBIT 5

Date: June 8, 1995

From: Director, Center for Biologics Evaluation and Research

Subject: Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma

To: All Registered Blood Establishments

The Food and Drug Administration (FDA) has periodically issued recommendations to blood establishments on donor deferral to prevent the transmission of infectious diseases, including Human Immunodeficiency Virus (HIV), Hepatitis B Virus, and Hepatitis C Virus, by blood and blood products. In April 1992, FDA issued two memoranda: "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products", and "Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)". These recommendations have not addressed the collection and use of Whole Blood, blood components, Source Leukocytes, and Source Plasma from inmates of correctional institutions. This topic has been reviewed recently by the FDA due to a series of recent reports.

One of the known risk factors associated with the transmission of HIV and hepatitis viruses is the use of illicit intravenous drugs involving needle sharing1-5. Reports by the U.S. Department of Justice6-14, the Centers for Disease Control and Prevention15-20, and others21-26, indicate that a significant proportion of inmates of correctional institutions are at increased risk of infectious

diseases because of their use of illicit intravenous drugs prior to incarceration. In a study of almost 17,000 intravenous drug users (IVDU) conducted between 1987 and 1989, 83% reported having been incarcerated in a prison or jail, and 78% reported sharing drug-injection equipment with another IVDU16. These data correlate with a high rate of infection with blood borne agents, including HIV and hepatitis viruses, and other transmissible agents in inmates entering or incarcerated in correctional facilities6-10,14,15,17-20,27-38. Consistent with this observation, the aggregate Acquired Immunodeficiency Syndrome incidence rate for State and Federal correctional systems in a 1992-1993 survey was 362 cases per 100,000 compared with 18 cases per 100,000 U.S. population8. Other risk factors for HIV and hepatitis transmission, such as tattooing39-41, and high risk sexual activity8,41,42, have been reported for inmates of prisons or jails. Although reports vary on the rate of seroconversion for HIV in the prison setting8,43-45, transmission of HIV and HBV have been reported in the prison environment.8,43,44,46

This information suggests that a history of incarceration in a correctional institution is associated with behaviors, such as intravenous drug abuse, that indicate an increased risk for transfusion-transmitted infections. In addition, for current inmates the nature of the prison environment may lead to a denial of behavioral risk factors by those seeking to donate blood products, because of secondary gains.47

The FDA therefore recommends that:

1. Current inmates of correctional institutions (including jails and prisons) and individuals who have been incarcerated for more than 72 consecutive hours during the previous 12 months be deferred as donors of Whole Blood,

blood components, Source Leukocytes, and Source Plasma for 12 months from the last date of incarceration.

2. Blood establishments supplement the AIDS education and self-exclusion material to include self-deferral from Whole Blood, blood components, Source Leukocytes and Source Plasma donations for donors who were incarcerated at a correctional institution for more than 72 consecutive hours within the previous 12 month period.

3. Blood establishments revise donor suitability standard operating procedures (SOPs) to incorporate these recommendations.

FDA recognizes that special public health needs may require collections from high risk donors. Establishments seeking approval for Whole Blood, blood components, Source Leukocytes or Source Plasma collections from inmates of correctional institutions and persons incarcerated for more than 72 hours within the previous 12 month period should submit Product and Establishment License applications or supplements for such collections. FDA will consider approval of such applications for in-vitro, or other special uses, when there are no alternative sources, consistent with its existing policy on collections from high risk donors. See, "Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ('High Risk' Donors)", 1989.

The recommendations contained in this memorandum may be implemented as soon as feasible, without prior approval from the Agency. For licensed establishments, a copy of the revised SOP should be submitted to the license file and should include the date of implementation.

For further information, contact Mary Gustafson, Director, Division of Blood Applications (HFM-375), FDA, 1401 Rockville Pike, Rockville, MD. 20852. (301) 594-2012.

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Kathryn C. Zoon, Ph.D.

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EXHIBIT 6

Guidance for Industry

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2007

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Guidance for Industry

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue- Based Products (HCT/Ps)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility determinations, with complying with the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C) (Ref. 1). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor-eligibility, including donor screening and testing, for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

This guidance applies to cells and tissues procured on or after the effective date of the regulations contained in 21 CFR part 1271, subpart C (effective date May 25, 2005). This guidance does not replace the guidance concerning 21 CFR part 1270, entitled "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," (Ref. 2), which remains applicable to tissues recovered before May 25, 2005 and subject to 21 CFR part 1270.

We recognize that some HCT/Ps (e.g., hematopoietic stem cells), as well as Whole Blood and blood components, can be collected by venipuncture from living donors. We encourage you to contact the Center for Biologics Evaluation and Research (CBER) should you have any questions as to the applicable regulatory framework for collection and further processing of such products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. What is the purpose of this guidance?

This guidance will assist establishments (HCT/P establishments) in complying with the requirements under 21 CFR part 1271, subpart C, for donor-eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases. These requirements apply to all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90.

This guidance finalizes the draft guidance, "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated May 2004," (Ref. 3). This guidance also finalizes the draft guidance, "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated June 2002 (Ref. 4).

B. What is the scope of this guidance?

This guidance is intended for: (1) Establishments responsible for performing any part of donor eligibility screening or testing, or for making donor-eligibility determinations; and (2) establishments that determine that an HCT/P meets release criteria and make the HCT/P available for distribution.

Establishment, as defined under § 1271.3(b), means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps. This includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of HCT/Ps, and includes facilities that engage in contract manufacturing. An establishment may engage another establishment under a contract, agreement, or other arrangement for screening and testing donors and for determining whether donors are eligible. Such allocations of responsibilities must comply with § 1271.150(c)[1].

[1] See Food and Drug Administration, Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements, dated September 2006. http://www.fda.gov/cber/guidelines.htm.

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III. THE DONOR-ELIGIBILITY DETERMINATION (§ 1271.50)

A. What is a donor-eligibility determination?

A donor-eligibility determination is a conclusion that a donor is either eligible or ineligible to donate cells or tissues to be used in an HCT/P, based on the results of donor screening (§ 1271.75) and testing (§§ 1271.80 and 1271.85). Except in certain situations specified under §§ 1271.60(d), 1271.65(b), and 1271.90, an HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible (§ 1271.45(c)).

Under § 1271.50(b), a donor is eligible only if:

- Screening shows that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases, and is free from communicable disease risks associated with xenotransplantation; and
- Test results for relevant communicable disease agents are negative or nonreactive, except as provided in § 1271.80(d)(1) for non-treponemal screening tests for syphilis.

B. Who makes the donor-eligibility determination?

In accordance with § 1271.50(a), a "responsible person" must determine and document the eligibility of a cell or tissue donor. A responsible person is one who is authorized to perform designated functions for which he or she is trained and qualified (§ 1271.3(t)). A responsible person should have appropriate medical training and adequate knowledge of relevant Federal regulations and guidances.

C. What are "relevant communicable disease agents or diseases (RCDADs)"?

There are two groups of relevant communicable disease agents and diseases. The first group consists of those communicable diseases and disease agents specifically listed in § 1271.3(r)(1). The second group consists of communicable diseases and disease agents described under § 1271.3(r)(2), that are not specifically listed in § 1271.3(r)(1). These two groups are as follows:

1. Relevant communicable disease and disease agents specifically listed in § 1271.3(r)(1).

a. The following communicable diseases and disease agents are relevant for all types of HCT/Ps (§ 1271.3(r)(1)(i)):

- Human immunodeficiency virus (HIV), types 1 and 2;
- Hepatitis B virus (HBV);
- Hepatitis C virus (HCV);
- Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD)[2]; and
- *Treponema pallidum* (syphilis).

b. The following cell-associated communicable disease or disease agents are relevant for viable, leukocyte-rich cells and tissues, including reproductive cells or tissues if they are considered to be viable leukocyte rich (see section VI.B.2. of this document) (§ 1271.2(r)(1)(ii)):

- Human T-lymphotropic virus (HTLV), types I and II.

c. The following communicable disease agents or diseases of the genitourinary tract are relevant for reproductive cells or tissues (§ 1271.3(r)(1)(iii)):

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea.*

2. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 1271.3(r)(1), is relevant if it is one:

a. For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with the HCT/P, such as medical personnel, because the disease agent or disease:

i. is potentially transmissible by an HCT/P; and

ii. either (1) has sufficient incidence and/or prevalence to affect the potential donor population (§ 1271.3(r)(2)(i)(B)(*1*)), or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (§ 1271.3(r)(2)(i)(B)(*2*));

b. That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate

[2] Variant Creutzfeldt-Jakob disease (vCJD) is not specifically listed in § 1271.3(r)(1)(i), but is an example of human transmissible spongiform encephalopathy.

medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (§ 1271.3(r)(2)(ii)); and

c. For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available (§ 1271.3(r)(2)(iii)).

In summary, FDA considers: (1) Risk of transmission, (2) severity of effect, and (3) availability of appropriate screening measures or tests, in accordance with § 1271.3(r)(2), as factors in determining whether a communicable disease or disease agent, not listed under § 1271.3(r)(1), is relevant. The importance of these factors in determining relevance may be based on the clinical significance of the disease agent or disease. For example, *Ureaplasma urealyticum*, although highly prevalent and transmissible, is not considered a relevant communicable disease agent because its pathogenicity to reproductive cell and tissue recipients has low clinical significance. However, we require screening for TSEs and screening or testing for HIV-2, although less prevalent, because they pose extremely significant health risks.

D. What communicable disease agents or diseases, not listed in § 1271.3(r)(1), have been determined to be relevant?

We have determined the following communicable disease agents and diseases, not specifically listed under § 1271.3(r)(1), to be relevant under § 1271.3(r)(2). This determination was based on the risk of transmission, severity of effect, and availability of appropriate screening measures or tests as described in section III.C. of this document. A brief discussion of these factors is provided under each relevant disease and agent listed. Additional background information is provided in the appendix, as indicated.

West Nile Virus (WNV)

Risk of Transmission: There is a risk of transmission of WNV by HCT/Ps. This is supported by observations of WNV transmission via organ transplantation, and via blood and blood product transfusion. Although it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5). (See Appendix 6).

Severity of Effect: WNV could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for WNV, such as the medical history interview and clinical evidence (see Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral). (Screening measures for WNV are discussed in sections IV.E. and IV.F. of this document.)

A donor screening test for WNV, using NAT technology, has been licensed for use in living and cadaveric HCT/P donors. IND studies are also ongoing for the development of other NAT screening tests for WNV (see section VI.A. and Appendix 6).

Sepsis

Risk of Transmission: There is a risk of transmission by HCT/Ps of any agent that could cause sepsis. The agents that cause sepsis include various bacterial, fungal, and viral agents. These agents have sufficient incidence and/or prevalence to affect the potential HCT/P donor population and are potentially transmissible. For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock (see Appendix 6).

Severity of Effect: Sepsis could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Mortality from sepsis is substantial, as sepsis is now among the top ten leading causes of death in the United States (see Appendix 6).

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for detection of sepsis, such as the medical history interview, and clinical and physical evidence. (Screening measures for sepsis are discussed in sections IV.E., IV.F. and IV.G. of this document.)

Vaccinia

Risk of Transmission: There is a risk of transmission of vaccinia (the virus used in smallpox vaccine) by HCT/Ps. Vaccinia has sufficient incidence and/or prevalence to affect the potential donor population, especially in light of current small pox vaccination programs. Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, two different investigators reported that vaccinia virus could sometimes be isolated from a patient's blood 3 to10 days after vaccination (Ref. 8). These studies did not use the less virulent New York

City Board of Health (NYCBOH) strain of vaccinia virus that comprises currently available vaccines in the United States. Other investigators using the NYCBOH strain of vaccinia virus were only able to detect virus in the blood of patients with disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination (see Appendix 6).

Severity of Effect: Vaccinia virus could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Historically, for every million people vaccinated in the past, up to 52 people have had a life-threatening reaction to smallpox vaccine and up to two people per million vaccinated have died (Refs. 10 and 11).

The potential consequences of vaccinia infection include severe complications (see Appendix 4). These consequences are more likely to occur in HCT/P recipients who are immunocompromised or who have burns or other serious skin conditions. Vaccinia virus infection rarely causes severe complications such as encephalitis and severe generalized vaccinia in otherwise healthy people. Also, the route of infection could influence the severity of the disease, so that it is possible that vaccinia infection transmitted via HCT/Ps could result in different or more severe infections than when acquired percutaneously (Ref. 12).

Availability of Appropriate Screening and/or Testing Measures: There are appropriate screening measures, such as the medical history interview, and clinical and physical evidence (see Ref. 12 for further information regarding the background and rationale for vaccinia deferral). (Screening measures for vaccinia are discussed in sections IV.E., IV.F. and IV.G. of this document.)

E. How will FDA handle other emerging infectious diseases in regard to HCT/P donor eligibility?

We intend to notify you through a guidance, if we determine that an infectious disease meets the definition of a relevant communicable disease under § 1271.3(r)(2). The guidance would include our comments or recommendations for donor screening and testing. We also intend to notify you through a guidance, if we conclude that a disease identified as "relevant" under § 1271.3(r)(2), no longer meets the criteria as a "relevant" disease for purposes of the donor eligibility regulations. In suitable situations, we will hold public meetings or consult with advisory committees to help us identify communicable disease agents or diseases for which donor screening and testing must be performed under §§ 1271.75, 1271.80, and 1271.85.

F. What procedures must I establish and maintain?

You must establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility, and complying with all other requirements of part 1271, subpart C (§ 1271.47(a)). A responsible person must review and approve all procedures before their implementation (§ 1271.47(b)). These procedures must be readily available to personnel in the area where the procedures are performed, or if this is not practical, in a nearby area (§ 1247(c)).

Under § 1271.47(d), at the time a departure occurs, you must record and justify that departure from a procedure relevant to preventing risks of communicable disease transmission. Before distributing an HCT/P manufactured under a departure from a procedure, a responsible person must determine that the departure did not increase the risk of communicable disease transmission.

We consider a departure to be an intended change from an established procedure, including a standard operating procedure (SOP), which occurs before the HCT/P is distributed, and is consistent with applicable regulations and standards. For example, a departure might include the use of a different manufacturer's reagents because the usual manufacturer's reagents were not available at the recovery site. In this example, although the use of the different manufacturer's reagent might represent a change from the established procedures, the change might be consistent with applicable regulations, standards, or established specifications. A departure is different from an HCT/P deviation, which under § 1271.3(dd) is defined as an event that is inconsistent with applicable regulations, standards, or established specifications, or is unexpected or unforeseeable.

You are authorized under §1271.47(e) to use appropriate standard procedures developed by another organization, provided that you have verified that the procedures are consistent with and at least as stringent as the requirements in part 1271. For example, you may use a current donor medical history questionnaire developed by a professional organization, provided that you have reviewed the questionnaire and determined that it meets the requirements for donor screening.

G. What records must accompany the HCT/P after the donor-eligibility determination has been completed?

Under § 1271.55(a) you must provide the following records with each HCT/P, after the donor-eligibility determination has been completed:

- A distinct identification code (such as an alphanumeric code) affixed to the HCT/P container, that relates the HCT/P to the donor and to all records pertaining to the HCT/P and, except in the case of autologous donations, directed

reproductive donations, or donations made by first-degree or second-degree blood relatives, does not include an individual's name, social security number, or medical record number;
- A statement whether, based on the results of screening and testing, the donor is determined to be eligible or ineligible; and
- A summary of the records used to make the donor-eligibility determination.

Under 1271.55(b), the summary of records in § 1271.55(a)(3) must include:

- A statement that the communicable disease testing was performed by a laboratory or laboratories: (1) certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or (2) meeting equivalent requirements, as determined by the Centers for Medicare and Medicaid Services (CMS);
- A listing and interpretation of the results of all tests performed for relevant communicable disease agents or diseases, and, if applicable, for CMV (§ 1271.85(b)(2))[3];
- The name and address of the establishment that made the donor-eligibility determination; and
- A statement noting the reason for the determination of ineligibility in the case of an HCT/P from a donor who is ineligible based on screening and released under § 1271.65(b).

The records referenced in § 1271.55 must accompany an HCT/P when it is placed into distribution (as defined in § 1271.3(bb)), including distribution that occurs within the same facility (e.g., peripheral blood stem/progenitor cells are collected within a facility's cell processing laboratory and are then sent to a patient's floor in that same facility). Once the consignee receives the accompanying records with the HCT/P, it is not necessary that those records physically accompany the HCT/P into the operating room or at the bedside (except for any information that is affixed to the HCT/P container). You should make accompanying records available for review by any medical personnel needing access to those records in order to provide patient care. Electronic access to accompanying records within a facility would satisfy the regulatory requirements under § 1271.55(a), as long as they are in compliance with § 1271.55(c) – deletion of personal information.

[3] If a repeat anonymous semen donor has multiple tests for CMV and during this time he seroconverts (he initially tests CMV negative and subsequently tests CMV positive), then in the summary of records you should indicate the CMV positive result, or you may provide information about all CMV test results.

Records that must accompany an HCT/P shipped under quarantine are discussed in section III.J. of this document.

H. What records must I retain, and for how long?

Under § 1271.55(d)(1), you must retain records of results and interpretation of all testing for relevant communicable disease agents and screening for communicable diseases, the name and address of the testing laboratory, and the donor eligibility determination, including the name of the responsible person who made the donor eligibility determination, and the date of the determination.

Under § 1271.55(d)(2), all records must be accurate, indelible, and legible.

Under § 1271.55(d)(4), you must retain records pertaining to a particular HCT/P for at least 10 years after the date of its administration. This includes records created by laboratories performing donor eligibility testing (§§ 1271.55(d)). If the date of administration is not known, then you must retain records at least 10 years after the date of distribution, disposition, or expiration, whichever is latest (§ 1271.55(d)(4)). Testing laboratories that are not aware of the date of administration, distribution, disposition or expiration, should retain records for at least 10 years after the record was created (i.e., after the testing was performed).

I. What do I do with the HCT/Ps before the donor-eligibility determination has been completed?

Before the completion of the donor-eligibility determination, you must keep an HCT/P in quarantine and clearly identify it as in quarantine (§ 1271.60(a) and (b)). The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution (§ 1271.60(b)).

Quarantine means the storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation (§ 1271.3(q)). An example of automated designation is the use of a validated computer system to maintain information on bar-code-labeled HCT/Ps held in a freezer. When you release the HCT/P, the computer system is activated to assure identification and retrieval of the specific HCT/P for the intended recipient.

J. May I ship an HCT/P that is in quarantine?

Yes, you may ship an HCT/P before completion of the donor-eligibility determination (§

1271.60(c)). However, in accordance with § 1271.60(c), the HCT/P must be kept in quarantine and must be accompanied by records that:

- Identify the donor (e.g., by a distinct identification code affixed to the HCT/P container), but not by name, social security number, or medical record number (except in the case of an autologous, or directed reproductive donors, or donations made by first-degree or second-degree blood relatives § 1271.55(a)(1));
- State that the donor-eligibility determination is not complete; and
- State that the HCT/P must not be implanted, transplanted, infused, or transferred until the donor-eligibility determination is complete, except in cases of urgent medical need under § 1271.60(d), and described in section VIII.C. of this document.

K. How do I store HCT/Ps from a donor who has been determined to be ineligible?

Under § 1271.65(a), if a donor is determined to be ineligible you must store or identify the HCT/Ps from the ineligible donor in a physically separate area clearly identified for such use, or follow other procedures that are adequate to prevent improper release, until the HCT/Ps are destroyed or distributed for use in certain limited circumstances identified in § 1271.65 (b) and (c), and described in section VIII.D. of this document. Examples of ways in which you may comply with this requirement, include employing separate refrigerators or freezers, using separate shelves in a single refrigerator or freezer, and using an automated designation system.

In accordance with § 1271.47(a), you must describe in your standard operating procedures (SOPs) the method you choose to store or identify the HCT/Ps from the ineligible donor.

IV. DONOR SCREENING (§ 1271.75)

A. For what diseases or conditions must I screen cell and tissue donors?

Under § 1271.75(a), you must screen a cell and tissue donor by reviewing relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases; and communicable disease risks associated with xenotransplantation, unless an exception identified in § 1271.90(a) applies. For donors of viable, leukocyte-rich cells or tissue, you must also screen for HTLV (§ 1275.75(b)). You must also screen donors of reproductive cells and tissue for the additional diseases identified as relevant to those HCT/Ps in § 1271.75(c). (See section III.C. of this document for discussion of relevant communicable disease agents and diseases.)

B. How do I screen a donor who is one month of age or younger?

Under § 1271.75, you must screen all donors, including infant donors one month of age or less, except as provided under §1271.90. Since a donor who is one month of age or younger cannot participate in the donor medical history interview, you must interview another individual able to provide the information sought in the interview (§ 1271.3(n)(2)).

You should also screen the birth mother when an infant is one month of age or less. Donor screening of the birth mother should involve a donor medical history interview and review of available medical records; the physical examination or physical assessment of the birth mother is recommended when practical.

C. What sources of information do I review?

When you screen a potential cell or tissue donor, you must review "relevant medical records" for risk factors for, and clinical evidence of, the relevant communicable diseases listed in § 1271.75(a)(1). Risk factors are described in section IV.E., clinical evidence in section IV.F., and physical evidence in section IV.G.

Relevant medical records, as defined under § 1271.3(s), means a collection of documents that includes: (1) a current donor medical history interview; (2) a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and (3) other available records listed in §1271.3(s)(1) through (4). We describe these three elements as follows:

1. The donor medical history interview (§ 1271.3(n)) is a documented dialogue concerning the donor's medical history and relevant social behavior:

a. With a living donor; or

b. If the donor is not living or is unable to participate in the interview, then with one or more individuals who can provide the information sought. These individuals might be:

- The donor's next of kin;
- The nearest available relative;
- A member of the donor's household;
- An individual with an affinity relationship with the donor (e.g., caretaker, friend, partner); or
- The donor's primary treating physician.

In accordance with § 1271.47, you must establish and maintain standard operating

procedures to assure that receipt and review of relevant medical records are properly conducted. In addition, for medical records created for the purpose of assisting in determining donor eligibility, such as records of the donor medical history interview and the report of a physical assessment of a cadaveric donor, you must establish and maintain SOPs to assure that such records are current, complete, and reliable.

The medical history interview may take place in person or by telephone.

Since a donor medical history interview is a documented dialog (§ 1271.3(n)), if a donor medical history questionnaire is self-administered, the interviewer should review and verify the answers with the individual who has filled out the questionnaire form.

2. The purpose of the physical assessment of a cadaveric donor or the physical examination of a living donor is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease. For a cadaveric donor, the physical assessment means a limited autopsy, or a recent antemortem or postmortem physical examination (§ 1271.3(o)). For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health care professionals (see section IV.G. of this document for discussion about physical evidence). Because this is a step in determining donor eligibility, you must establish and maintain standard operating procedures (SOPs) for the conduct of the physical assessment or physical examination (§ 1271.47).

3. If they are available, the following other records also meet the definition of relevant medical records (§ 1271.3(s)).

- Laboratory test results (other than the results of testing required for the donor-eligibility determination);
- Medical records;
- Coroner and autopsy reports; and
- Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease). Examples of these records include: medical examiner reports, police records, and information from other tissue or medical establishments, if applicable.

You should make inquiries into these records and other information when the circumstances indicate that follow-up information might be relevant for screening a potential cell or tissue donor. For example, when reviewing the relevant medical

records, including the medical/social history interview, the tissue bank might find information to suggest that the donor might have been incarcerated, pursued by the police, or been under police investigation, or that the cause of death resulted in a police report (e.g., fatal gunshot wound). If that is the case, the tissue bank should make inquiries to obtain all relevant information regarding the eligibility of the donor, which is available from and disclosable by the police department.

We define "available" to mean that a record or information exists, or is pending, and can be obtained through due diligence, within a reasonable amount of time. A "reasonable" amount of time is a period of time that would allow for the collection of important information without compromising the utility of the tissue. Examples of these terms are as follows:

Example 1: A living donor brings his medical records with him to the screening site. These records are available, and you would review them.

Example 2: A cadaveric donor dies as a result of an event that leads to the creation of a police report. If the police report was disclosable to you within a reasonable period of time, you would review it.

Example 3: You know that an autopsy report will be prepared on a cadaveric donor, but the report will not be complete for several weeks. If waiting several weeks to review the autopsy report would compromise the utility of the tissue, perhaps because your HCT/P (e.g., cornea) needs to be released within a limited timeframe, then the report could not be obtained in a reasonable time period. Under these circumstances, it might not be necessary to wait to review the final report of autopsy results before distribution of the HCT/P. If this is the case, you should use the available information when considering the donor's eligibility, including the presumed cause of death and other relevant preliminary autopsy findings and all other information obtained about the donor. Also, you should review the final autopsy report when it becomes available. If any new information in the final report indicates that the donor is ineligible, you should consider notifying the consignees of the distributed HCT/Ps and submit to FDA an HCT/P deviation report within 45 days, if applicable.

D. When may I perform an abbreviated donor screening procedure?

Section 1271.75(e) states, "If you have performed a complete donor screening procedure on a living donor within the previous 6 months, you may use an abbreviated donor screening procedure on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior."

If you perform an abbreviated screening:

- You do not need to conduct a new physical examination or a new review of relevant medical records.
- You should remind the donor about behaviors that could put him/her at risk of a relevant communicable disease. If any new behavioral risk has been identified in the interval since the last donation, you should also address that new behavioral risk.
- We do not require that this information be presented in any specific way. Possible methods include the use of a pamphlet or a wall chart, or other effective means of communication.
- You should then ask the donor if there have been any changes in donor history or risk factors since the previous donation.

If you wish to perform an abbreviated donor screening procedure, you must have conducted a complete donor screening procedure on the living donor (including donor history questionnaire, physical examination, and review of any new medical records, if applicable) within 6 months prior to the abbreviated procedure (§ 1271.75(e)).

E. What risk factors or conditions do I look for when screening a donor?

For all donors, you must review the relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for relevant communicable disease agents and diseases, and communicable disease risks associated with xenotransplantation (§ 1271.75(a)).

Following is a list of conditions and behaviors that increase the donor's relevant communicable disease risk. Except as noted in this section, and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following conditions or behaviors.

1. Men who have had sex with another man in the preceding 5 years (Refs. 17 through 46) (risk factor for HIV and Hepatitis B).

2. Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections (Refs. 18, 21, 22, 25, 27, 29, 33, 34, 36, 38, 42, and 45 through 59) (risk factor HIV, Hepatitis B and Hepatitis C).

3. Persons with hemophilia who have received human-derived clotting factor concentrates in the preceding 5 years (Refs. 18 and 60) (risk factor for HIV, Hepatitis B and Hepatitis C).

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4. Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years (Refs. 18, 21, 22, 24, 25, 27, 29, 33, 34, 38, 40, 44, 45, 46, 61, 62, and 63) (risk factor for HIV, Hepatitis B and Hepatitis C).

5. Persons who have had sex in the preceding 12 months with any person described in criteria 1 through 4 of this section or with any person who has HIV infection, including a positive or reactive test for HIV virus (Refs. 17 and 18), hepatitis B infection (Ref. 64), or clinically active (symptomatic) hepatitis C infection (Refs. 65 and 66).

6. Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 18 and 64).

7. Children born to mothers with or at risk for HIV infection:

- If 18 months of age or younger, or
- If breast-fed within the preceding 12 months.

Note: We do not recommend deferral of a donor who is a child born to a mother with or at risk for HIV infection if the child is over 18 months of age and has not been breast-fed within the preceding 12 months, provided that the child's HIV antibody tests, physical examination, and medical records do not indicate evidence of HIV infection (Ref. 18).

8. Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months (Refs. 29, 67, and 68) (risk factor for HIV, Hepatitis B and Hepatitis C).

9. Persons who have lived with (resided in the same dwelling) another person who has hepatitis B or clinically active (symptomatic) hepatitis C infection in the preceding 12 months (Ref. 69).

10. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used (Ref. 69).

11. Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday (Refs. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as being caused by hepatitis A virus, Epstein-Barr Virus (EBV), or cytomegalovirus (CMV).

12. Persons who are deceased and have a documented medical diagnosis of sepsis

or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death. For example, if a statement such as "rule-out sepsis" is noted in the medical records, and subsequent notations indicate a diagnosis other than sepsis, a potential donor might still be eligible.

13. Persons who have had smallpox vaccination (vaccinia virus) in the preceding 8 weeks (Ref. 12) should be evaluated as follows:

a. For persons who had no vaccinia complications (see Appendix 4 for definition of vaccinia complication):

- You should defer the donor until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date, and until the physical examination or physical assessment includes a confirmation that there is no scab at the vaccination site.
- In cases where a scab was removed before separating spontaneously, you should defer the donor for two months after vaccination.

Note: We do not recommend deferral of a cadaveric donor who was vaccinated at least 21 days ago and who has no visible scab, if you are unable to obtain a history of how the scab separated.

b. For persons who have experienced vaccinia complications (see Appendix 4), you should defer the donor until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had vaccinia complications but who currently has no visible signs of vaccinia complications, if you are unable to obtain a history of the exact date of resolution of the vaccinia complications.

14. Persons who acquired a clinically recognizable vaccinia virus infection by contact with someone who received the smallpox vaccine (i.e., touching the vaccination area or the scab, including the covering bandages, or touching clothing, towels, or bedding that might have come into contact with an unbandaged vaccination area or scab) (Ref. 12).

- For living donors who developed skin lesions as a result of contact with someone who received the smallpox vaccine, you should question the donor regarding the loss of the scab, and you should examine the skin. For cadaveric donors, you should examine the skin.
- If no scab is present, we do not recommend deferral of:
    - a cadaveric donor;

- a living donor if the scab spontaneously separated; or
- after three months from the date of vaccination of the vaccine recipient, a living donor whose scab was otherwise removed.

- If a scab is present, you should consider:
  - a cadaveric donor to be ineligible; or
  - a living donor to be deferred until the scab spontaneously separates.

You should defer persons who developed other complications of vaccinia infection acquired through contact with a vaccine recipient until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had complications of vaccinia acquired through contact with a vaccine recipient, but has no visible signs of vaccine complications, if the date of resolution of the vaccinia complications is unknown.

We do not recommend deferral of contacts who never developed skin lesions or other complications of vaccinia infection.

15. Persons who have had a medical diagnosis or suspicion of WNV infection (based on symptoms and/or laboratory results, or confirmed WNV viremia) you should defer for 120 days following diagnosis or onset of illness, whichever is later (Refs. 5, 6, and 7).

16. Persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days (Refs. 5 and 7).

17. Persons who have been treated for or had syphilis within the preceding 12 months. We do not recommend deferral of donors if evidence is presented that the treatment occurred more than 12 months ago and was successful.

18. Reproductive HCT/P donors who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection in the preceding 12 months. We do not recommend deferral of persons who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection if evidence is presented that the treatment occurred more than 12 months ago and was successful.

19. Persons who have been diagnosed with vCJD or any other form of CJD (Refs. 3 and 75).

Note: Numbers 19 to 26 in this section are designed to screen for TSEs, including CJD and vCJD. If the living donor or the individual knowledgeable about the donor's medical and travel history is not familiar with the term "Creutzfeldt-Jakob Disease"

or "variant Creutzfeldt-Jakob Disease," you may try to describe those in layman's terms. If the person being interviewed is still not familiar with those terms, you may consider the lack of familiarity with those terms as a negative response to questions using those terms.

20. Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or other neurological disease of unknown etiology (Refs. 3 and 75). Potential donors who have a diagnosis of delirium (e.g., delirium caused by toxic/metabolic diseases or recent head trauma) would not necessarily be considered to have a diagnosis of dementia and should be evaluated by the Medical Director. (HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident or brain tumor and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director).

21. Persons who are at increased risk for CJD (Refs. 3 and 75). Donors are considered to have an increased risk for CJD if they have received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD (see criterion 22 of this section).

22. Persons who have a history of CJD in a blood relative (Refs. 3 and 75) unless:

- The diagnosis of CJD was subsequently found to be an incorrect diagnosis;
- The CJD was iatrogenic; or
- Laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

23. Persons who spent three months or more cumulatively in the United Kingdom (U.K.) (see Appendix 5) from the beginning of 1980 through the end of 1996 (Refs. 3 and 75).

24. Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996 (Refs. 3 and 75).

25. Persons who spent 5 years or more cumulatively in Europe (see Appendix 5) from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996) (Refs. 3 and 75).

26. Persons who received any transfusion of blood or blood components in the

U.K. or France between 1980 and the present (Refs. 3 and 75).

27. Persons or their sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

28. Persons who have received a blood transfusion or any medical treatment that involved blood in the countries listed in criterion 30, after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

Note: Establishments utilizing an HIV antibody test that has been approved by FDA for detection of HIV group O viruses may delete criteria 27 and 28 from their screening procedures. All other establishments should continue to use these recommended deferral criteria. You can find a list of donor screening tests that have been licensed for use with cadaveric specimens on CBER's website: http://www.fda.gov/cber/tissue/prod.htm. We intend to update the website periodically as additional tests are labeled for this use and become available.

29. Persons who are xenotransplantation product recipients or intimate contacts of a xenotransplantation product recipient (Ref. 77).

a. For the purpose of this document, we define the following terms:

i. Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (1) live cells, tissues, or organs from a nonhuman animal source; or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

ii. Xenotransplantation products include live cells, tissues, or organs used in xenotransplantation. Biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.

iii. Xenotransplantation product recipient means a person who undergoes xenotransplantation.

iv. Intimate contact of a xenotransplantation product recipient means a person who has engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with a xenotransplantation product recipient. Examples of intimate contacts include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct

exposures. We do not consider sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, to be intimate contact.

b. To determine whether a potential HCT/P donor is a xenotransplantation product recipient, or is the intimate contact of a person who has received a xenotransplantation product, you should determine whether the potential donor, his/her sexual partner, or any member of his/her household has ever had a transplant or other medical procedure that involved being exposed to live cells, tissues, or organs from an animal. If the potential donor or his/her sexual partner is the recipient of a xenotransplantation product, you should defer the donor. If the potential donor is a member of the xenotransplantation product recipient's household, you should determine whether the potential donor has been exposed to blood, saliva, or other body fluids from the xenotransplantation product recipient. If the potential donor has been exposed to any of these fluids, you should defer the donor.

Note: There are circumstances in which it might not be necessary to defer a potential HCT/P donor who is an intimate contact of a recipient of certain xenotransplantation products. For example, an advisory committee recommended and we concur that intimate contacts of persons who have received the product Epicel™ do not need to be deferred from blood donation, because the risk of zoonotic transmission from this product is minimal as the non-human animal cells used in the manufacture of this product originate from a well-characterized cell line. For this same reason, intimate contacts of Epicel™ recipients need not be deferred from tissue donation (Ref. 78) (Note: You should defer Epicel™ recipients from tissue donation).

F. What clinical evidence do I look for when screening a donor?

You must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (§ 1271.75). For cadaveric donors, you should:

- Determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, or,
- If an autopsy was performed, whether any special precautions were taken that would suggest there was special concern over the risk of transmission of a communicable disease from the donor.

You should look for the following examples of clinical evidence of relevant communicable disease. Except as noted in this section and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following examples of clinical evidence of relevant communicable

disease.

1. HIV infection:

   - A prior positive or reactive screening test for HIV;
   - Unexplained weight loss;
   - Unexplained night sweats;
   - Blue or purple spots on or under the skin or mucous membranes typical of Kaposi's sarcoma;
   - Disseminated lymphadenopathy (swollen lymph nodes) for longer than one month;
   - Unexplained temperature of > 100.5°F (38.6°C) for more than 10 days;
   - Unexplained persistent cough or shortness of breath;
   - Opportunistic infections;
   - Unexplained persistent diarrhea; and/or
   - Unexplained persistent white spots or unusual blemishes in the mouth (Ref. 79).

2. Hepatitis infection:

   - A prior positive or reactive screening test for hepatitis B virus or hepatitis C virus;
   - Unexplained jaundice;
   - Hepatomegaly; and/or
   - Past diagnosis of clinical, symptomatic viral hepatitis after the 11th birthday (Ref. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as caused by hepatitis A virus, EBV, or CMV.

Note: Records of the following laboratory data might assist you in making the donor-eligibility determination in the face of an inconclusive history of hepatitis infection: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or prothrombin time (Ref. 71). If these tests are abnormal, but a cause other than viral hepatitis was established, we do not recommend that you defer the donor.

3. Syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* infection (Screening and donor deferral for *Chlamydia trachomatis* and *Neisseria gonorrhea* required only for reproductive donors):

   - Persons who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* in the preceding 12 months (Ref. 79).

We do not recommend deferral of donors who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* more than 12 months ago, if evidence is presented that treatment occurred more than 12 months ago and was successful (Ref. 80).

4. Vaccinia infection (see IV. E., 13. and 14. for specific deferral criteria for recent smallpox vaccination or acquired vaccinia infection by contact with someone who received the smallpox vaccine):

- Recent smallpox vaccination;
- Eczema vaccinatum;
- Vesicular rash indicative of generalized vaccinia in a person who has had recent smallpox immunization or who is a contact of someone with recent smallpox immunization, as specified in IV. E. 14.;
- Progressive necrosis in an area of vaccination consistent with vaccinia necrosum;
- Postvaccinial encephalitis; and/or
- Vaccinial keratitis (Ref. 12).

5. WNV infection (Refs. 5, 6, and 7). Because signs and symptoms of WNV can be nonspecific, you should consider the following clinical evidence in light of other information obtained about the donor in making a donor eligibility determination.

- Mild symptoms might include fever, headache, body aches, or eye pain;
  - mild symptoms might also occasionally be accompanied by a skin rash on the trunk of the body; or
  - swollen lymph glands.
- Severe illness;
  - severe illness might include encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis;
  - signs and symptoms of severe illness might include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, and muscle weakness or paralysis.

6. Sepsis (includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) or septic shock):

In reference to deceased donors, if any of these conditions is specifically diagnosed in the medical records during a hospital stay immediately preceding death, you should determine the donor to be ineligible (see section IV.E. criterion 12 of this document). If a living donor appears healthy, the donor usually does not need to be evaluated for sepsis.

Sepsis may be described by the following clinical evidence (Ref. 84). You should consider these signs in light of other information obtained about the donor in making a donor eligibility determination.

- Clinical evidence of infection; and
- Two or more of the following systemic responses to infection if unexplained:
  - Temperature of >100.4° F (38° C);
  - Heart rate >90 beats/min;
  - Respiratory rate >20 breaths/min or PaCO2 <32; or
  - WBC >12,000 cells/mm^3, < 4,000 cells/mm^3, or >10% immature (band) forms.
- More severe signs of sepsis include unexplained hypoxemia, elevated lactate, oliguria, altered mentation, and hypotension.
- Positive (pre-mortem) blood cultures might be associated with the above signs.

7. HTLV infection:

   - A prior positive or reactive screening test for HTLV;
   - Unexplained paraparesis; and/or
   - Adult T-cell leukemia (Refs. 85 and 86).

G. What physical evidence do I look for?

Relevant medical records (§1271.3(s)) include the report of the physical assessment of a cadaveric donor (§1271.3(o)) or the physical examination of a living donor. For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health professionals. You should review the records of the physical assessment or physical examination for any of the following signs that may indicate high-risk behavior for or infection with a relevant communicable disease. Some of the following are not physical evidence of HIV, hepatitis, syphilis, or vaccinia but rather are indications of high-risk behavior associated with these diseases and would increase the donor's relevant communicable disease risk. Except as noted in this section and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following examples of physical evidence of relevant communicable disease or high-risk behavior associated with these diseases (see Refs. 12 and 87).

1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, chancroid (you should consider these signs in

light of other information obtained about the donor in making a donor eligibility determination) (seen in HIV, Hepatitis B virus, *Chlamydia trachomatis*, and *Neisseria gornorrheae*).

2. Physical evidence for risk of, or evidence of syphilis.

3. For a male donor, physical evidence of anal intercourse including perianal condyloma (seen in HIV and Hepatitis B).
4. Physical evidence of nonmedical percutaneous drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (seen in HIV, Hepatitis B and Hepatitis C).

5. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 12 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used (seen in HIV, Hepatitis B and Hepatitis C).

6. Disseminated lymphadenopathy (seen in HIV).

7. Oral thrush (seen in HIV).

8. Blue or purple spots consistent with Kaposi's sarcoma (seen in HIV).

9. Unexplained jaundice, hepatomegaly, or icterus (seen in Hepatitis B and Hepatitis C).

Note: Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed.

10. Physical evidence of sepsis, such as unexplained generalized rash or fever.

11. Large scab consistent with recent history of smallpox immunization.

12. Eczema vaccinatum (seen in vaccinia).

13. Generalized vesicular rash (generalized vaccinia).

14. Severely necrotic lesion consistent with vaccinia necrosum.

15. Corneal scarring consistent with vaccinial keratitis.

Contains Nonbinding Recommendations

V. DONOR TESTING: GENERAL (§ 1271.80)

A. What requirements apply to laboratories performing donor testing for relevant communicable disease agents or diseases?

1. Under § 1271.1, you must be registered with FDA.

2. Under § 1271.80(c):

   - You must use appropriate FDA licensed, approved or cleared donor screening tests, if such tests are available, in accordance with the manufacturer's instructions.
   - You must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available.
   - You must be certified to perform such testing on human specimens either under the Clinical Laboratory Improvement Amendments (CLIA) or you must meet equivalent requirements as determined by the Centers for Medicare and Medicaid Services. Examples of the latter include laboratories that have been accredited by accrediting organizations approved by CMS. Certain states are exempt under CLIA because CMS has found their state programs to be in compliance with CLIA standards.[4] Information about the CLIA program is available at the website: http://www.cms.hhs.gov/clia/.

3. Under §§ 1271.55(d), you must maintain documentation of results and interpretation of all testing for at least 10 years.

B. What type of test must I use?

You must test using an appropriate FDA-licensed, approved, or cleared donor screening test (if applicable to your HCT/P and available) in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of the

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[4] CMS has approved the following accrediting organizations:AABB, the American Osteopathic Association, the American Society for Histocompatibility and Immunogenics, the College of American Pathologists, COLA, and the Joint Commission on Accreditation of Healthcare Organizations. CMS has determined two states to be exempt: New York and Washington. Since these lists are subject to change, we recommend that you consult CMS for the most current information. http://www.cms.hhs.gov/clia/.

relevant communicable disease agent or disease (§ 1271.80(c)).

- You should choose a test that is adequate, appropriate and available for detecting the relevant communicable disease agent or disease. We list tests that we currently consider to meet the requirements in §1271.80(c) in section VI. of this document.
- In some instances, you may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. For example, to test for HIV-1, it is appropriate to use a test that detects viral nucleic acid (e.g., a nucleic acid test) and a test that detects antibody to HIV-1 (e.g., an enzyme immunoassay). If HIV-1 infection is present, each test may be reactive at different times during the course of the disease.
- If you are testing a specimen of cadaveric blood (i.e., taken from a donor whose heartbeat has ceased), you must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test, when such a test is applicable and available (§ 1271.80(c)). You can find a list of donor screening tests that have been licensed for use with cadaveric specimens on CBER's website: http://www.fda.gov/cber/tissue/prod.htm. We intend to update the website periodically as additional tests are licensed, cleared or approved for this use and become available.

C. How do I perform the test and interpret test results?

You must perform the test according to the manufacturer's instructions in the test kit's package insert (§ 1271.80(c)). The manufacturer's instructions also provide information about interpretation of test results.

Some HCT/P establishments routinely rely solely on the test results obtained by an organ procurement organization (OPO), while other establishments routinely perform their own donor testing with the awareness that OPOs are performing donor testing on the same donors. The use of an appropriate screening test, performed in accordance with the manufacturer's instructions for use, would satisfy the requirements of §§ 1271.80 and 1271.85. However, because of testing practices related to organ donor screening as described by the Centers for Disease Control and Prevention (CDC), some OPOs may run an enzyme immunoassay donor screening test initially in triplicate (Ref. 18). The manufacturer's instructions for use of HCT/P donor screening tests currently do not provide instructions for initial triplicate testing, interpretation of test results of such testing, or for retesting after an initially reactive test when the tests are initially run in triplicate. Therefore, if initial tests are run in triplicate and one or more reactive results are obtained, manufacturers do not provide instructions on determining whether the sample is actually (repeatedly) reactive. Accordingly, if you engage an OPO to perform testing for you or if you routinely perform your own tests but are aware that an OPO is also performing tests on that donor, and that OPO performs initial testing in triplicate,

then under §§ 1271.50 and 1271.150 you must obtain and review the results of all three tests performed by that OPO. If any of those initial tests is reactive or positive, then the donor would not be eligible to donate.

D. If a donor is one month of age or younger, from whom must I collect a specimen?

If a donor is one month of age or younger, you must collect and test a specimen from the birth mother instead of the donor (§ 1271.80(a)). The specimen for testing from the birth mother may be collected within seven days of donation by the infant (§ 1271.80(b)). If a specimen from the birth mother of a donor one month of age or younger is unavailable, the donor is ineligible. Specimens collected for any infant donor more than one month of age, including adopted infants, should be collected from the donor rather than the birth mother.

E. When do I collect a specimen for testing?

You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or within seven days before or after the recovery of cells and tissue (§ 1271.80(b)), with some exceptions as described in this section. As you are permitted under §1271.80(b) to collect the donor specimen up to seven days before recovery of cells or tissues, you may use a premortem specimen to test a cadaveric donor, as long as the specimen is collected within that timeframe.

In the case of donation of hematopoietic stem/progenitor cells (HPCs) obtained from peripheral blood or bone marrow (if not excepted under §1271.3(d)(4)), we realize that the recipient may begin myeloablative chemotherapy more than 7 days before the transplant. Therefore, the identified allogeneic donor might need to be qualified before this time, including screening and testing of the donor for relevant communicable diseases. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (§ 1271.80(b)(1)).

In the case of donation of oocytes that do not undergo a period of cryopreservation prior to implantation, an oocyte donor might need to be qualified before the 7 days prior to donation due to the time necessary for receiving hormonal stimulation. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (§ 1271.80(b)(1)).

Although there is no requirement that specifies when to test the collected specimen, you should perform testing as soon as possible after collection and in accordance with the time limits stated in the manufacturer's instructions for use of the test kit.

F. May I test a specimen from a donor who has undergone transfusion or infusion?

Transfusion or infusion might dilute plasma, making test results unreliable (Refs. 18 and 88). You may test a specimen taken before the transfusion or infusion and up to seven days before recovery of cells or tissue, or if an adequate pre-transfusion/infusion specimen is not available, you may use an appropriate algorithm to determine whether plasma dilution is or is not sufficient to affect test results. In the absence of an appropriate specimen to test under either of these options, you must determine the donor to be ineligible (§ 1271.80(d)(2)).

For adult donors who have suffered blood loss sufficient to require fluid replacement, certain volumes of transfusions and/or infusions (described in section V.F.1. of this document) should be suspected of affecting test results. Blood loss might occur internally or externally. For donors 12 years of age or younger, you should suspect that any transfusion or infusion might affect test results regardless of blood loss. There might be other clinical situations involving transfusion or infusion that should also be suspected of affecting test results. Autologous blood removed pre-operatively or peri-operatively and reinfused during the same surgical procedure would not need to be included in plasma dilution calculations.

1. Adult Donor (§ 1271.80(d)(2)(ii)(A))

In accordance with § 1271.80(d)(2)(ii)(A), you must suspect plasma dilution sufficient to affect the results of communicable disease agent testing where blood loss is known or suspected in a donor over 12 years of age in any of the following situations:

a. The donor received a transfusion or infusion of more than 2000 milliliters of blood (e.g., whole blood or red blood cells) or colloids either: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen for testing is collected post-mortem, whichever occurred earlier.

b. The donor received more than 2000 milliliters of crystalloids within either: (i) the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if the specimen for testing is collected post-mortem, whichever occurred earlier.

c. The donor received more than 2000 milliliters of any combination of whole blood, red blood cells, colloids, and/or crystalloids within the applicable time frames set out in paragraphs (a) and (b) in this section.

2. Pediatric Donor (§ 1271.80(d)(2)(ii)(B))

In accordance with § 1271.80(d)(2)(ii)(B), you must suspect plasma dilution

sufficient to affect the results of communicable disease agent testing, regardless of the presence or absence of blood loss, in a donor 12 years of age or under, in any of the following situations.

a. Any transfusion of blood or colloids: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.
b. Any crystalloids: (i) within the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.

3. Other Clinical Situations

We cannot provide guidance that anticipates every possible clinical situation where plasma dilution might affect test results. As the establishment that collects donor specimens for testing, you might be aware of additional circumstances in which plasma dilution might affect test results. Your SOPs should identify any additional circumstances where you believe plasma dilution might have occurred, and you should use a pre-transfusion/infusion specimen or apply an algorithm in those instances.

Examples: In the following situations, the donor has received a transfusion or infusion, but circumstances are not otherwise consistent with the examples set out in sections V.F.1. and 2. of this document. Nevertheless, you should consider test results on specimens collected at the time of donation to be potentially unreliable, triggering the need to test a pre-transfusion or pre-infusion sample, or to apply the algorithm, in the following circumstances:

- A donor who has previously had blood loss, stabilizes, then expires, but has received fluids in the 48 hours before specimen collection;
- A donor who is obese;
- A donor who in the absence of bleeding may have received large amounts of infusions which the medical director or designee believes may affect test results;
- A donor who weighs less than 45 kilograms or more than 100 kilograms.

For situations falling outside those described in your SOPs, but where plasma dilution is still suspected, your SOPs should indicate how the situation would be handled (for example, by consulting the medical director).

4. Pre-Transfusion/Infusion Specimen

As part of establishing procedures for all steps in testing in accordance with § 1271.47(a), establishments making donor eligibility determinations must have SOPs that define those elements necessary to determine whether a pre-transfusion/infusion blood specimen is adequate for infectious disease testing (e.g., the amount of hemolysis, storage conditions, and age of the specimen). Testing laboratories must perform tests in accordance with the manufacturer's instructions (§ 1271.80(c)), including any instructions concerning factors that might affect specimen stability.

5. Algorithms

An appropriate algorithm must evaluate the fluid volumes administered in the 48 hours before collecting the specimen from the donor and show that plasma dilution sufficient to affect test results has not occurred (§ 1271.80(d)(2)(i)(B)). A plasma dilution of greater than 50% (1:2 dilution) could make test results unreliable. Therefore, you should use a method that compares the actual fluid volumes administered with both the donor's plasma and blood volumes to assess whether a greater than 50% dilution has occurred.

If the algorithm shows that greater than a 50% dilution has occurred, then you should not use the post-transfusion/infusion specimen for testing. You should not use further procedures that attempt to qualify the ineligible specimen.

When calculating blood and plasma volumes for donors in the 45 to 100 kilogram range, where there is blood loss with replacement, you should calculate and assess both blood volume and plasma volume as follows:

- Determine the blood volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.015, or alternatively by multiplying the body weight in kilograms by 70 mL/kg.
- Determine the plasma volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.025, or alternatively by multiplying the body weight in kilograms by 40 mL/kg.

(See Appendices 1, 2, and 3)

G. What are some useful definitions related to hemodilution?

1. *Blood component* means a product containing a part of human blood separated by physical or mechanical means (§ 1271.3(i)).

2. *Colloid* means: (1) a protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic)

pressure in the intravascular compartment; or (2) blood components such as plasma and platelets (§ 1271.3(j)).

3. *Crystalloid* means an isotonic salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer's lactate solution, 5 percent dextrose in water (§ 1271.3(k)), or total parenteral nutrition (TPN) (Ref. 89).

4. *Plasma dilution* means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids (§ 1271.3(p)).

VI. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

You must test all donors of HCT/Ps, unless subject to an exemption in § 1271.90(a), for the diseases listed in section VI.A.1. through 5., as required in § 1271.85(a). You must use an FDA-licensed, approved, or cleared screening test, as described in section V. (§ 1271.80(c)). Current FDA-licensed donor screening tests for HIV, Hepatitis B, Hepatitis C, and HTLV are listed at the website: www.fda.gov/cber/products/testkits.htm. You may also check this website: http://www.fda.gov/cber/tissue/prod.htm for links to HCT/P-related, FDA-licensed, approved or cleared donor screening tests. The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable disease. Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. HIV, type 1[5] (FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2 (Refs. 79 and 90); and FDA-licensed screening NAT test[5] for HIV-1, or combination NAT); (establishments not utilizing an FDA-licensed screening test that tests for group O must defer donors at risk for HIV group O infection as described in section IV.E.30. and 31. (Refs. 66 and 76))

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[5] At the time of publication of this guidance, there are no currently licensed or approved donor screening NAT tests that have an indication for use to include testing of HCT/P donor specimens (living or cadaveric) in pools. The only donor specimens that have an indication for use to test in pools are specimens from donors of whole blood, blood components, and source plasma.

Contains Nonbinding Recommendations

2. HIV, type 2[5] (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2) (Refs. 79 and 90);

3. HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) (Ref. 72) and for total antibody to Hepatitis B core antigen (anti-HBc)(IgG and IgM) (Refs. 91 through 98);

4. HCV (FDA-licensed screening test for anti-HCV[6]; and FDA-licensed screening NAT test for HCV, or combination NAT) (Refs. 2, 69, 90, 91, and 99); and

5. *Treponema pallidum* (FDA-cleared screening test) (Refs. 80 and 100).

As an exception for syphilis test results under §1271.80(d)(1), you may determine to be eligible a donor whose specimen tests reactive (or positive) on a screening test for syphilis and negative or nonreactive on a confirmatory test (e.g., fluorescent treponemal antibody with absorption test (FTA-ABS), so long as all other required testing and screening are negative or nonreactive. A donor whose specimen tests positive or reactive on a confirmatory test is not eligible. If a cadaveric specimen is too hemolyzed to interpret the RPR test result, you may use the FTA-ABS test result.

Discussion of Assay Results

a. Nontreponemal assays, such as the Venereal Disease Research Laboratory (VDRL) test, the Rapid Plasma Reagin (RPR) test, and the Automated Reagin Test (ART), detect nonspecific antibodies (Reagin) to an antigen called cardiolipin present in host tissues as well as in treponemes. These assays are useful in monitoring the progression of disease and response to therapy. However, positive or reactive tests might be due to diseases other than syphilis (i.e., biological false positives). Samples that give positive or reactive results using nontreponemal assays may be retested using a treponemal-based assay as a confirmatory assay, such as the FTA-ABS. Nontreponemal test results usually become nonreactive within a year or two after successful treatment of syphilis.

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[6] On July 22, 2004, FDA approved the Abbott Laboratories Supplement to their Biological License Application for Hepatitis C Virus Encoded Antigen to modify the intended use of the Abbott HCV EIA 2.0 to include the testing of cadaveric specimens. This specifically labeled test kit is now available for commercial use.

b. Treponemal assays incorporate specific treponemal antigens into the testing system and detect specific antibodies to these antigens. With a few exceptions, unlike nontreponemal assays, results of tests for treponemal antigens remain positive or reactive for specific antibodies throughout an individual's life, even after successful treatment for syphilis. Treponemal assays include the FTA-ABS, the *Treponema pallidum* immobilization test (TPI) and the *T. pallidum* hemagglutination assay (TPHA). In general, treponemal assays have a higher sensitivity in detecting primary and late syphilis than do nontreponemal assays. However, as both types of assays detect antibodies, they might not identify some very early syphilis infections before antibodies to either cardiolipin or specific treponemal antigens have appeared (Ref. 100).

c. Donor screening tests for syphilis may be either non-treponemal or treponemal-based assays. We are aware that there are pre-Amendments devices that may be marketed for use in donor screening. These tests, along with cleared donor screening tests for syphilis, are acceptable for use in donor screening. Because of the potential for false-positive results in non-treponemal assays or persistent positive tests in treponemal-based assays after successful treatment for syphilis, FDA-approved or cleared confirmatory testing may be used to determine the syphilis status of a potential HCT/P donor. If the confirmatory test is positive or reactive, the donor is ineligible.

6. p24 Antigen Tests: We are aware that HIV-1 p24 antigen tests are not readily available because they are not currently being manufactured. Therefore, you are not required to use the HIV-1 p24 antigen test for HCT/P donors. There are currently more sensitive tests available (Refs. 90 and 101).

Discussion About Additional Testing

You or someone else might perform additional testing not listed in section VI.A. If you perform donor testing for relevant communicable diseases using tests in addition to those listed in section VI.A.1. through 5., VI.B., and VI.C., as applicable, or if you are aware that other establishments are performing such tests and the test results are available, such test results must be included in the donor's relevant medical record (see § 1271.3). Because these test results are part of the medical record, you must consider any results from those tests when you make a donor eligibility determination (§ 1271.75(a)). By "available" we mean that the test result exists or is obtainable within a reasonable amount of time. A "reasonable" amount of time is a period of time that would not compromise the utility of the tissue.

Example: An eye bank is aware that a tissue bank performs an investigational NAT assay on a shared donor. The eye bank is not informed of the test results until after the corneas need to be released in order to maintain their utility. The eye bank does not have to wait for the investigational NAT results before

releasing the corneas. The eye bank should inform the consignee that the investigational NAT results are pending, and subsequently report the result.

Confirmatory tests: You should consider performing confirmatory tests when a positive or reactive screening test result is received for such purposes as donor counseling or investigating discordant test results. However, if you perform a confirmatory test, negative or nonreactive results on a confirmatory test would not override a positive or reactive screening test (except for syphilis tests as previously described in this section).

Example: A potential donor's specimen tests reactive for antibody to HCV. However, a confirmatory test (e.g., radioimmunoblot assay) is negative. The donor would be considered ineligible despite the negative confirmatory test.

Hepatitis B surface antibody (anti-HBs) test: If you obtain a positive or reactive anti-HBs test and other markers for Hepatitis B infection are negative or non-reactive, the donor may be eligible.

Example: Your contract laboratory routinely performs three different tests for HBV: Hepatitis B surface antigen (HBsAg) test, Hepatitis B core antibody (anti-HBc) test, and anti-HBs test. You have a potential donor who is negative or nonreactive for HBsAg and anti-HBc, but positive or reactive for anti-HBs. The presence of anti-HBs alone would not disqualify the donor, because it usually is an indication of vaccination against Hepatitis B. However, in this situation, if the anti-HBc were also positive or reactive, the donor is ineligible. Data suggests that such results can be associated with infectivity (Refs. 92 through 98).

B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use?

1. You must test donors of viable, leukocyte-rich cells or tissue for the following diseases, in addition to those listed in section VI.A. of this document (§ 1271.85(b)). You must use an FDA-licensed, cleared, or approved donor screening test where such a test is available (§ 1271.80(c)). A list of currently licensed donor screening tests for HCT/Ps can be found at the website: http://www.fda.gov/cber/tissue/prod.htm.

The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable diseases:

a. Human T-lymphotropic virus, types I and II (FDA-licensed screening test for anti-HTLV I/II) (Refs. 85 and 86).

b. Cytomegalovirus (FDA-cleared screening test for anti-CMV) (total IgG and IgM).

Special note on CMV: CMV is not a relevant communicable disease agent or disease. However, establishments are required to test donors of viable, leukocyte-rich cells or tissues for CMV. A donor who tests positive or reactive for CMV (total antibody) is not necessarily ineligible to donate HCT/Ps. You must establish and maintain an SOP regarding donors whose specimens test positive or reactive for CMV (§ 1271.85(b)(2)). This latter requirement only applies to establishments that make available for distribution HCT/Ps for which CMV testing is required.

Establishments should include procedures in their SOPs for communicating test results of donors who are positive or reactive for CMV antibody (total). The SOP should at least specify how the CMV test results should be communicated to the physician responsible for accepting the HCT/P. For example, the SOP should require that this information appear in materials accompanying the HCT/P, so that physicians may rely on this information to make informed decisions about the use of an HCT/P in a particular recipient's situation. An establishment's SOPs may also clarify that repeated testing of donors who are positive or reactive for CMV antibody (total) is unnecessary once it is established that a particular donor is positive or reactive, so long as this information is contained in the summary of records.

2. Examples of viable, leukocyte-rich cells or tissue include, but are not limited to:

- Hematopoietic stem/progenitor cells
- Semen

You should consider cells and tissues to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing might remove leukocytes.

3. Examples of cells or tissue that are not considered viable, leukocyte-rich cells or tissues include, but are not limited to:

- Corneas
- Sclera
- Skin
- Heart valves
- Dura mater
- Bone
- Tendons
- Ligaments
- Cartilage

- Oocytes

Under § 1271.45(b), in the case of embryos or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor. Therefore, although an embryo might not be considered leukocyte-rich, when an embryo is transferred to an individual who is not a sexually intimate partner, the semen donor should be tested for HTLV types I and II and for CMV.

C. How do I assess a donor of dura mater for TSE?

You must perform an adequate assessment for donors of dura mater to detect evidence of TSE (§ 1271.85(e)). After the dura mater has been removed, you should have a qualified pathologist perform an examination of the donor's brain. Following fresh examination, the brain should be fixed and sliced, gross examination of the entire brain should be conducted (including multiple cross sections), and multiple specimens of tissue should be obtained (from different parts of the brain) for histological examination. Exclude potential donors when any possible evidence of TSE-related changes is observed on histological examination. There are currently no FDA-licensed, approved, or cleared donor screening tests for prions.

VII. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, AND 1271.85)

A. Do I need to screen and test all donors of reproductive cells and tissue?

Except as provided in § 1271.90, you must screen and test all directed reproductive donors (as defined in § 1271.3(l)) and anonymous donors of reproductive cells and tissues (§§ 1271.75, 1271.80, and 1271.85) (Refs. 102 through 138).

B. What additional screening must I do for donors of reproductive cells and tissue?

In addition to the screening required for all cell and tissue donors and, if applicable, the screening requirements for viable, leukocyte-rich cell and tissue donors, you must review the relevant medical records of donors of reproductive HCT/Ps (who are not sexually intimate partners) for risk factors for and clinical evidence of infection due to relevant sexually transmitted and genitourinary diseases that can be transmitted with the recovery of the reproductive cells or tissue (§ 1271.75(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea.*

Specific donor screening recommendations are described in section IV. of this document.

C. What additional testing must I perform on donors of reproductive cells and tissue?

In addition to the testing required for all cell and tissue donors, and, if applicable, the testing required for donors of viable, leukocyte-rich cells and tissues, you must test donors of reproductive HCT/Ps (who are not sexually intimate partners) for evidence of infection due to relevant genitourinary disease agents (§ 1271.85(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea.*

Special note on *Chlamydia trachomatis* and *Neisseria gonorrhea* testing: Although there are diagnostic tests available, there are currently no FDA-licensed, approved, or cleared tests for donor screening. In the absence of such screening tests, you must use an FDA-licensed, approved, or cleared diagnostic test labeled for the detection of these organisms in an asymptomatic, low-prevalence population (§ 1271.80(c)). FDA recommends *Chlamydia trachomatis* and *Neisseria gonorrhea* test kits utilizing NAT technology to adequately and appropriately reduce the risk of infectious disease transmission (Refs. 81, 139 through 148). You can find a listing of FDA-licensed or approved test kits for *Chlamydia trachomatis* and *Neisseria gonorrhea* at the following website: http://www.fda.gov/cber/tissue/prod.htm.

Exception from testing requirement:

If the reproductive cells or tissue are recovered by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* are not required (§ 1271.85(c)). However, if these tests are performed and one or both results are reactive, the donor must be determined ineligible, regardless of the recovery method used (§ 1271.80(d)(1)).

D. What follow-up testing is required for anonymous semen donors?

At least 6 months after the donation, you must collect a new specimen from the anonymous semen donor and repeat testing required under § 1271.85(a) through (c) (§ 1271.85(d)). You must quarantine the donated semen until the retesting is complete and the donor is determined to be eligible (§ 1271.60(a)). See IV. D. for a discussion of screening of repeat donors.

Note: If a repeat anonymous semen donor discontinues donations, you should wait at least 6 months from the final donation and re-test the donor for all RCDADs in order to

qualify the final donation, except that you may use the results of tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* obtained at the final donation, or any time later than that, as the test of record to qualify that final donation.

Example: A donor tests negative or nonreactive for HBsAg and Hepatitis B core antibody. He is retested 6 months later, and is still negative or nonreactive for HBsAg, but is positive or reactive for Hepatitis B core antibody. The donor is ineligible. The semen in quarantine should not be transferred to an anonymous recipient.

E. Is follow-up testing required for directed donors of semen?

No, we do not require follow-up testing when semen is donated for directed use. Specimens collected for use in donor eligibility testing must be collected within 7 days of each collection (§ 1271.80(b)). You may alternately elect to perform quarantine of semen and retesting of the directed donor as described for anonymous semen donors in section VII.D. of this document (§ 1271.85(d)), rather than performing donor testing within 7 days of each collection.

F. Is a donor eligibility determination required for gestational carriers or surrogate carriers?

No. Gestational or surrogate carriers are not considered to be donors according to the FDA definition of a donor (§1271.3(m)). Gestational or surrogate carriers are considered to be HCT/P recipients.

G. Is a donor eligibility determination required for donors of reproductive cells and tissues that are transferred to gestational or surrogate carriers?

Section 1271.45(b) states that in the case of an embryo or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor. In complying with screening and testing requirements when embryos are involved, you should consider the relationship between the gestational carrier and the oocyte and semen donors separately in order to determine which donor eligibility requirements apply.

The following examples assume that when the embryos were formed, they were intended for transfer to a gestational carrier.

Example: A gestational carrier known to a couple will carry an embryo formed from the woman's oocyte and a mixture of semen from the man and an anonymous donor. The embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so both members of

the couple are considered directed donors (§ 1271.3(l)).
- A donor eligibility determination must be made for both members of that couple (§ 1271.45(b)), but the use of reproductive cells or tissue from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65 (b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).
- The other semen donor is not known to the gestational carrier, so that donor is considered an anonymous donor and must have a donor eligibility determination (§ 1271.3(l)). If the semen donor is ineligible, the semen may not be used (§ 1271.45(b)).
- Quarantine of the anonymous donor's semen and retesting of the anonymous semen donor is required (§§ 1271.60(a) and 1271.85(d)).

Example: A gestational carrier known to a couple will carry an embryo formed from an oocyte donated by a donor who is known to the couple, but not to the gestational carrier, and semen from a member of that couple. The embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so the semen donor in this situation would be a directed donor (§ 1271.3(l)).
- A donor eligibility determination must be made for the directed semen donor each time he donates semen, but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).
- The oocyte donor is known to the couple but not known to the gestational carrier, so the donor is considered an anonymous donor (§ 1271.3(l)).
- The oocyte donor must have a donor eligibility determination (§ 1271.45(b)). If the oocyte donor is ineligible, the oocytes may not be used (§ 1271.45(c)).

Example: A surrogate carrier is known to a couple. The surrogate's oocyte(s) and semen from a member of that couple will be used to form embryo(s) that will be carried for the couple by the surrogate.

- No donor eligibility determination is required for the surrogate.
- The couple is known to the surrogate, so the semen donor would be a directed donor (§ 1271.3(l)).
- A donor eligibility determination is required for the semen donor each time he donates semen (§ 1271.45(b)), but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).

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VIII. EXCEPTIONS FROM THE REQUIREMENTS FOR DETERMINING DONOR ELIGIBILITY AND SPECIAL CIRCUMSTANCES (§§ 1271.90, 1271.60(d), 1271.65(b), AND 1271.65(c))

This section describes: (1) situations when you are not required to perform a donor-eligibility determination; (2) situations in which the donor-eligibility determination is incomplete; and (3) situations in which the use of cells or tissue from a donor who has been determined to be ineligible is not prohibited. These situations require special labels. We define the term "label" when used in this guidance and in §§ 1271.60(d), 1271.65(b), and 1271.90(b), to mean either (1) a printed label affixed to the HCT/P container, or (2) a printed label affixed as a tie-tag to the HCT/P container. However, if it is not physically possible to comply with (1) or (2), either because the container is too small to affix all of these labels to the container, or because the container is frozen, and therefore affixing the labels or attaching a tie-tag is not feasible, then the "Warning" statements in sections VIII.B.3., 5., and 6. of this document may accompany the HCT/P.

A. When is a donor eligibility determination not required? (§ 1271.90)

There are five situations in which you are not required to make a determination of donor eligibility or to perform donor screening and testing (§ 1271.90(a) and §1271.15(a)). You must apply special label requirements if you do not screen and test (§ 1271.90(b)).

Donor eligibility determinations are not required (§ 1271.90(a) (1) through (4)) for:

1. Cells and tissue for autologous use (§ 1271.90(a)(1));

2. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use (§ 1271.90(a)(2);

3. Cryopreserved cells or tissue for reproductive use, other than embryos, exempt at the time of donation as described in 1 and 2, above, that are subsequently intended for directed donation, provided that

a. additional donations of suitable cells and tissues are unavailable due to the infertility or health condition of a donor of the cryopreserved reproductive cells or tissue; and
b. appropriate measures (see note after section VIII.A.4. of this document) are taken to screen and test the donor(s) before transfer to the recipient (§ 1271.90(a)(3)).

This exception addresses the situation where the donor was not screened and tested at the time of cryopreservation of the reproductive cells or tissue, and where the donor cannot make additional donations (e.g., the woman is post-menopausal or has had her ovaries or uterus removed, or because the man has undergone chemotherapy which

renders him infertile). The donor wishes to make a directed donation of the cryopreserved semen or oocytes to someone the donor knows. Under these circumstances, you should screen and test the donor at least six months after recovery of the cryopreserved HCT/Ps and before the donation is made. In such cases, as in other cases involving directed donations of reproductive tissue, we would not prohibit the use of an HCT/P from an ineligible directed donor (section VIII.D.2. of this document).

4. A cryopreserved embryo, originally excepted under § 1271.90(a)(2) at the time of cryopreservation, that is subsequently intended for directed or anonymous donation. When possible, you should take appropriate measures (see note after section VIII.A.4. of this document) to screen and test the semen and oocyte donors before transfer of the embryo to the recipient (§ 1271.90(a)(4)).

This exception addresses the situation where sexually intimate partners were not screened and tested at the time of cyropreservation of their embryos, and later wish to make a directed or anonymous donation of their cryopreserved embryo(s). Under these circumstances, you should cryopreserve the embryos for at least 6 months and when the decision is made to donate the embryo(s) to an individual or a gestational carrier, you should screen and test the semen and oocyte donors when possible. In such cases, as in other cases involving directed donations of reproductive tissue (section VIII.D.2. of this document), the use of embryos from an ineligible directed donor is not prohibited. In addition, although FDA requires appropriate screening and testing when possible, if appropriate screening and testing are not possible (e.g., because one of the donors is unavailable), you may still transfer the embryo into a recipient. Labeling requirements apply, regardless of whether the semen and oocyte donors were screened and tested (those labeling requirements are described in section VIII.B. of this document).

Because one of the gamete donors would already have been found eligible, FDA also intends to apply this policy to a sexually intimate couple's cryopreserved embryos where one of the gametes is from a qualified (i.e., eligible) third party gamete donor, and the other gamete is from the sexually intimate partner of the intended recipient. In this circumstance, you should also screen and test the sexually intimate partner gamete donor when possible, and labeling requirements would apply.

Note: By "appropriate measures", we mean that you screen and test the donor(s) for those communicable disease agents for which a donor of such reproductive cells or tissue would ordinarily be tested at the time of donation, and a donor eligibility determination be made, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea*. The reason is that testing for *Chlamydia trachomatis* or *Neisseria gonorrhea* at the time of donation of the reproductive cells or tissue would not provide information about the status of the donor(s) for these agents at the time of the earlier cryopreservation.

To meet the donor testing requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., if the donor(s) cannot be tested due to death or inability to locate the donor, you should use the most recent available specimen from the donor(s) to perform the appropriate testing.

To meet the donor screening requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., if the donor(s) cannot be interviewed in person due to death or inability to locate the donor(s), then the donor medical history interview may be performed with another individual as described in § 1271.3(n), and section IV.C. of this document.

5. In accordance with §1271.15(a), you are not required to make a determination of donor eligibility or to perform donor screening and testing if you are an establishment that uses HCT/Ps solely for nonclinical scientific or educational purposes (see section VIII.E. for those labeling requirements). The § 1271.90 labeling requirements do not apply.

B. What special labeling is required for HCT/Ps that are excepted under the provision of § 1271.90(a) from the donor eligibility determination (§ 1271.90(b)(1)through (6))?

Note: More than one of the following label requirements may apply to a particular HCT/P.

1. For HCT/Ps excepted under § 1271.90(a)(1), if the HCT/Ps are stored for autologous use, then under § 1271.90(b)(1) you must label the HCT/Ps "FOR AUTOLOGOUS USE ONLY."

2. For HCT/Ps excepted under §1271.90(a)(1 through 4), if you do not test and screen a donor, then under § 1271.90(b)(2) you must label the HCT/Ps from that donor "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" unless you have performed all otherwise applicable screening and testing under §§ 1271.75, 1271.80, and 1271.85. For instance, if you perform some but not all of the testing and screening that would otherwise be required in these sections, or if you do not use a registered, CLIA-certified laboratory, or FDA licensed, cleared, or approved donor screening tests, this label would apply. This label would not apply to reproductive cells and tissue labeled in accordance with § 1271.90(b)(6).

Example 1: You must label an HCT/P from an autologous donor who has not been screened and tested under the exception in § 1271.90(a)(1), "FOR AUTOLOGOUS USE ONLY" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

Example 2: A man wishes to donate his stored semen to his sexually intimate partner. You test the man for HIV-1 and HIV-2 before he donates the semen to his sexually

intimate partner, but under the § 1271.90 (a)(2) exception you are not required to test for any of the other relevant communicable diseases for which anonymous or directed sperm donors would be required to be tested. If you do not perform all of the additional testing, you must label the stored semen "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

3. For HCT/Ps excepted under §1271.90(a)(2 through 4), (excluding HCT/Ps for autologous use), you must under § 1271.90(b)(3) label the HCT/P with "WARNING: Advise recipient of communicable disease risks" when either the donor eligibility determination has not been completed or if screening or testing indicates the presence of relevant communicable disease agents and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases.

4. For HCT/Ps excepted under §1271.90(a), if donor screening or testing indicates the presence of relevant communicable disease agents or diseases and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases, then under 1271.90(b)(4) you must label the HCT/P with the Biohazard legend shown in § 1271.3(h).

5. If HCT/Ps are recovered under § 1271.90(a) from donors who have positive or reactive test results for any relevant communicable disease agent or disease, then under § 1271.90(b)(5) you must label the HCT/P with "WARNING: Reactive test results for (name of disease agent or disease)."

6. If reproductive tissue will be donated to a directed recipient under § 1271.90(a)(3) or a directed or anonymous recipient under § 1271.90(a)(4), and the screening and testing is performed before transfer to the recipient rather than at the time of recovery, then under § 1271.90(b)(6) you must label the HCT/P, "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently." Before transfer, if you have not performed all otherwise applicable screening and testing under §§ 1271.75, 1271.80, and 1271.85, then § 1271.90(b)(2) would apply.

Example: HCT/Ps from a sexually intimate couple are used to form embryos. The partners were not required to be screened and tested (§ 1271.90(a)(2)). Some embryos are transferred to the female partner and other embryos are cryopreserved. It is determined that the female partner cannot carry a fetus to term. The couple then decides to transfer the cryopreserved embryos to a gestational carrier who is known to the couple.

- No donor eligibility determination is required for the gestational carrier.
- The couple agrees to be screened and tested now, in accordance with §§ 1271.75, 1271.80, and 1271.85, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea* (See note in section VIII. A. of

this document). They are both determined to be eligible.

- Under § 1271.90(b)(6), you must prominently label the HCT/P with the statement: "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently."
- The cryopreserved embryos are transferred to the gestational carrier.
- Note that if it was not possible to take appropriate measures to screen and test the donors (e.g., because one donor resides outside the United States and is unavailable) the embryos could nevertheless be transferred to the gestational carrier. In that case, the labeling would contain the statements: "Not evaluated for infectious substances" (§ 1271.90(b)(2)) and "Warning: Advise recipient of communicable disease risk" (§ 1271.90(b)(3)).

The records required under section § 1271.55 (see section III.G. of this document), including the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, based on the results of the screening and testing, and the summary of records are NOT required for HCT/Ps excepted under § 1271.90(a). The reason is that § 1271.55 applies only after a donor eligibility determination is complete, and this does not occur in the situations in § 1271.90. However, you should include this information, if known.

C. Can cells or tissue from a donor be used before the donor eligibility determination under §1271.50 (a) is completed?

Yes. The use of cells or tissues from a donor before the donor eligibility determination is completed, is not prohibited under § 1271.60(d) if there is a documented urgent medical need. However, you must comply with the following requirements under § 1271.60(d)(2) through (4).

1. If an HCT/P is made available based on a physician's request for urgent medical need before completing the donor-eligibility determination, you must document the urgent medical need and label the HCT/P prominently: "NOT EVALUATED FOR INFECTIOUS SUBSTANCES," and "WARNING: Advise patient of communicable disease risk."

2. The HCT/P must be accompanied by a statement of: (a) the results of any required donor screening that has been completed; (b) the results of any required testing that has been completed; and (c) a list of any required screening and testing that has not yet been completed.

3. The manufacturer of the HCT/P must document that the physician using the HCT/P was notified that the testing and screening were not complete.

4. You must complete the donor-eligibility determination during or after the emergency use of the HCT/P, and inform the physician of the results of the determination.

D. Can cells or tissue from an ineligible donor ever be used for implantation, transplantation, infusion, or transfer? (§ 1271.65(b))

Yes. Under §1271.65(b), an HCT/P from an ineligible donor, based on required testing and/or screening results, is not prohibited from use for implantation, transplantation, or transfer in the following three circumstances.

1. The HCT/P is for allogeneic use in a first-degree or second-degree blood relative. (Parents, children, and siblings are considered first-degree relatives. Aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren are second-degree relatives. Relations by adoption or marriage are not included);

2. The HCT/P consists of reproductive cells or tissue from a directed reproductive donor. (A directed reproductive donor means a donor of reproductive cells or tissue, including semen, oocytes, and embryos, to which the donor contributed the spermatozoa or oocyte, to a specific recipient, and who knows and is known by the recipient before donation. The term does not include a sexually intimate partner (§ 1271.3(l)); or

3. There is an urgent medical need for the HCT/P based upon a physician's request documented by the establishment. (An urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P (§ 1271.3(u)).

An HCT/P made available under these provisions from an otherwise ineligible donor must be labeled prominently with the Biohazard legend (§ 1271.3(h)) and with the statement "WARNING: Advise patient of communicable disease risk," and, in the case of reactive or positive test results, "WARNING: Reactive test results for (name of disease agent or disease)" (§1271.65(b)(2)). The records required under § 1271.55 must accompany the HCT/Ps used under § 1271.65(b). The records required under § 1271.55 (section III.G. of this document) include the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, and the summary of records. If the donor was determined to be ineligible based on screening, the summary of records must contain a statement noting the reason or reasons for the determination of ineligibility (§ 1271.55(b)(4)).

Moreover, if you are the manufacturer of an HCT/P used in the previously described circumstances, you must document that you notified the physician using the HCT/P of the results of screening and testing (§ 1271.65(b)(3)).

Note: If testing and screening are not required under the regulations, such as when a donor donates reproductive tissue to a sexually intimate partner, then the reproductive tissue may be donated in accordance with that exception, even if you know that the donor is otherwise ineligible.

E. Are there any other uses for human cellular and tissue-based HCT/Ps from donors determined to be ineligible?

Yes. The use of HCT/Ps from a donor determined to be ineligible, is not prohibited for nonclinical uses, so long as they bear the Biohazard legend and are labeled "For Nonclinical Use Only" (§ 1271.65(c)).

IX. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than 6 months after issuance of this guidance.

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Contains Nonbinding Recommendations

APPENDIX 1

EXAMPLE OF A FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR INFECTIOUS DISEASE TESTING

Donor transfused/infused-----*No*-----Test blood specimen

|

Yes

|

Donor is an adult-----*No*-----Recent pre-transfusion/infusion-----*Yes*-----Test pre-transfusion /infusion blood specimen (>12 years old) | blood specimen available

|

No

|

Yes Apply algorithm (See Appendix 2)

|

Recent pre-transfusion/infusion blood specimen available ------*Yes*------Test pre-transfusion/infusion blood specimen

|

No

|

Blood loss occurred-----*No*-----Test blood specimen

|

Yes

|

Are the following conditions exceeded:
1. 2000 mL blood or colloid within 48 hours or
2. 2000 mL crystalloids within 1 hour or
3. 2000 mL total combination of blood and colloid in last 48 hours with crystalloid in last hour ------*No*------Test blood specimen

|

Yes

|

Apply algorithm (see Appendix 2)

Contains Nonbinding Recommendations

ACCOMPANYING QUESTIONS FOR FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR INFECTIOUS DISEASE TESTING

Question #1 – Has the donor had a transfusion or infusion?

- If the answer to question # 1 is no, then test the blood specimen
- If the answer to question #1 is yes, then ask question #2

Question #2 – Is the donor an adult?

- If the answer to question #2 is no, then ask question #2a
- If the answer to question #2 is yes, then ask question #3

Question #2a – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is twelve years of age or younger?

- If the answer to question # 2a is no, then apply the algorithm (see appendix 2)
- If the answer to question #2a is yes, then test the pre-transfusion/infusion blood specimen that is available

Question #3 – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is more than twelve years of age?

- If the answer to Question #3 is yes, then test the pre-transfusion/infusion blood specimen
- If the answer to Question #3 is no, then ask Question #4

Question #4 – Has blood loss occurred?

- If the answer to Question #4 is no, then test the blood specimen
- If the answer to question number 4 is yes, then ask Question #5

Question #5 – Are any of the following conditions exceeded?

- 2000 mL of blood or colloid given to the donor within the past 48 hours;
- 2000 mL of crystalloids within the last hour; or
- 2000 mL total of any combination of blood and colloid within past 48 hours, and crystalloid within the past hour

- If the answer to Question #5 is no, then test the blood specimen
- If the answer to Question #6 is yes, then apply algorithm (see Appendix 2)

Contains Nonbinding Recommendations

APPENDIX 2

EXAMPLE OF AN ALGORITHM

DONOR ID # _____

Date and Time of Specimen Collection _____
Donor's weight in kg _____

A = Total volume of blood transfused in the 48 hours before death or sample collection, whichever comes first

B = Total volume of colloid infused in the 48 hours before death or sample collection, whichever comes first

C = Total volume of crystalloid infused in the 1 hour before death or sample collection, whichever comes first

BV = donor's blood volume

Calculated blood volume = donor's weight (kg) / 0.015 OR
donor's weight (kg) x 70 mL/kg

PV = donor's plasma volume

Calculated plasma volume = donor's weight (kg) / 0.025 OR
donor's weight (kg) x 40 mL/kg

Calculate both:

1. Is B + C > PV?
2. Is A + B + C > BV?

[Enter a zero if a category (A, B, or C) was not transfused/infused.]

Determination of Sample Acceptability for Infectious Disease Tests:

If the answers to both 1 and 2 are NO, the post-transfusion/infusion sample is acceptable.

If the answer to either 1 or 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

Contains Nonbinding Recommendations

APPENDIX 3

Example of a Plasma Dilution Worksheet (Using Appendix 2 Algorithm)

Donor ID # _____

Date and Time of Sampling..... _____ am/pm

Donor Weight in kg ..... _____ kg

Blood Volume (BV) = donor's weight (kg) _____ ÷ 0.015 .....

OR (BV) = donor's weight (kg) _____ X 70 mL/kg..... _____ mL

Plasma Volume (PV) = donor's weight (kg) _____ ÷ 0.025 .....

OR (PV) = donor's weight (kg) _____ X 40 mL/kg..... _____ mL

A. Total Volume of Blood Transfused/48 hours (before death or sample collection, whichever comes first)

Volume of: RBCs transfused/48 hours _____

+ whole blood transfused/48 hours _____ A = _____ mL

B. Total Volume of Colloid Infused/48 hours (before death or sample collection, whichever comes first)

Volume of: dextran _____ mL

+ plasma _____ mL

+ platelets _____ mL

+ albumin _____ mL

+ hetastarch _____ mL

+ Other _____ mL _____

_____ mL _____

B = _____ mL

C. Total Volume of Crystalloid Infused/1 hour (before death or sample collection, whichever comes first)

Volume of: saline _____ mL

+ Dextrose in water _____ mL

+ Ringer's lactate _____ mL

+ Other _____ mL _____

_____ mL _____ C = _____ mL

Determination of Sample Acceptability for Infectious Disease Tests:

[Calculate both 1. and 2. Enter a zero if a category (A, B, or C) was not transfused/infused]

1. Is B + C > PV? Y N

2. IS A + B + C > BV? Y N

* If the answers to both 1 and 2 are NO, the post-transfusion/infusion sample is acceptable
* If the answer to either 1 or 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

Contains Nonbinding Recommendations

APPENDIX 4

MODERATE AND SEVERE COMPLICATIONS OF SMALLPOX VACCINATION AND INADVERTENT VACCINIA VIRUS INFECTION

Complications of smallpox vaccine or of inadvertent vaccinia virus infection, for the purpose of this guidance, are defined as the following, and are consistent with CDC definitions of moderate to severe adverse reactions to the smallpox vaccine, or to inadvertent vaccinia virus infection in contacts of vaccine recipients (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm).

Eczema vaccinatum
Generalized vaccinia
Progressive vaccinia
Postvaccinial encephalitis
Vaccinial keratitis

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in someone with eczema (atopic dermatitis) or a history thereof, or with other chronic or exfoliative skin conditions.

Generalized vaccinia is characterized by a vesicular rash of varying extent that can occur among persons without underlying illnesses. The rash is generally self-limited and requires minor or no therapy except in rare cases, when the vaccine recipient is systemically ill.

Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic vaccinia lesions. It has occurred almost exclusively among persons with cellular immunodeficiency.

Postvaccinial encephalitis is a rare but serious complication of vaccinia virus infection.

Vaccinial keratitis is an infection of the cornea, which can cause corneal scarring and visual impairment. This condition is usually caused by accidental self-inoculation of the eye from the vaccine site, or from self-inoculation after contact with another vaccine recipient, and is not believed to be due to hematogenous spread or associated with a secondary viremia.

Contains Nonbinding Recommendations

APPENDIX 5

LIST OF BSE-AFFECTED COUNTRIES APPLICABLE TO DONOR DEFERRAL

European Countries to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

[1]For purposes of this guidance, the United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

Contains Nonbinding Recommendations

APPENDIX 6

West Nile Virus (WNV)

WNV was first identified in the United States in 1999, in an epizootic outbreak among birds and horses and an epidemic of meningitis and encephalitis in humans in the New York City area. Throughout 2000 - 2001, avian mortality surveillance documented geographic spread to about half of the United States. In 2001, 66 human cases of WNV encephalitis or meningitis occurred in 10 states. In 2002, a major epizootic outbreak of WNV was detected in many parts of the United States combined with the largest human WNV meningoencephalitis outbreak ever documented, and the largest outbreak of meningoencephalitis from any cause in North America. In 2002, the number of human cases far surpassed those reported in 2001 with 4,161 cases of WNV illness and 277 deaths reported as of March 12, 2003. Ninety-nine percent of the human cases occurred between July 1 and October 31, 2002. Human cases were reported in 736 counties in 39 states and the District of Columbia. The 2002 WNV epidemic involved the first documented cases of WNV transmission through organ transplantation, blood transfusion, and possibly breastfeeding (Refs. 149 and 150). In addition, intrauterine infection was reported (Ref. 151). Surveillance reports published weekly in Morbidity and Mortality Weekly Report (MMWR) indicated that WNV was active in the United States in 2003 and had spread to additional areas of the country as compared to 2002. Blood establishments began using WNV nucleic acid amplification tests (NAT) under investigational drug exemptions (IND) beginning late June 2003. It is estimated that, through 2004, at least 1017 presumptively viremic donations were removed from the blood supply as a result of blood establishments' voluntary participation in WNV NAT screening studies (Ref. 5). In 2003, a total of 9,862 cases of human illness, including 2,775 neuroinvasive disease cases and 264 fatalities were reported to CDC (Refs. 5, 152, 153, and 154). In the 2004 WNV epidemic, CDC reported WNV activity in 47 continental states, with 2,470 reported human cases and 88 fatalities (Refs. 5, 154, 155, and 156).

WNV has the potential to be spread via HCT/Ps, as evidenced by its transmission via organ transplantation, and via blood and blood product transfusion. Though it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5).

Our current recommendation is only for donor screening. Some HCT/P donors are being tested under the IND previously mentioned, though testing with an investigational product is not a requirement. In WNV infection, 80% of persons are asymptomatic, 20% have mild symptoms, and only about 1/150 persons experience severe illness. Because symptoms occur in only approximately 20% of persons infected with WNV, donor exclusions based on donor health screening will have limited effectiveness. Laboratory screening tests to detect donor infections with WNV will be needed if the epidemic persists. We may recommend routine use of appropriate licensed donor screening test(s) to detect acute infections with WNV using NAT

technology once such tests are available. (See Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral.)

Sepsis

For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock. The causative agent in sepsis has been changing over the years. Fungal pathogens have become an increasingly important cause of sepsis. Gram-negative organisms were the most common organisms leading to sepsis between 1979 and 1987, but, by 2000, gram-positive organisms caused 52.1% of cases and gram-negative organisms were responsible for about 37.6% (Ref. 157). Various bacterial, fungal, and viral agents have been shown to be transmissible via HCT/Ps (Refs. 158 through 162) and bacterial infection potentially resulting in sepsis with associated morbidity and mortality is a widely recognized risk from transfused blood and blood products (Refs. 163 and 164).

A recent study in the New England Journal of Medicine (NEJM) reviewed the epidemiology of sepsis in the United States from 1979 through 2000 by looking at discharge data contained in the National Hospital Discharge Survey (Ref. 157). This study showed that the incidence of sepsis has been increasing over that time period and estimated the incidence as of 2000 to be 240.4 cases/100,000 population. The NEJM study also cited references stating that sepsis is now among the top ten leading causes of death in the United States. Another widely cited sepsis study by Angus, et al. reviewed all the 1995 discharge data from a sample of hospitals in 7 states that collectively served approximately 25% of the population of the United States (Ref. 165). The Angus study estimated the incidence of sepsis over that year to be about 3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges. The Angus study estimated that in 1995, about 9.3% of all deaths in the United States were a direct or indirect result of sepsis – similar to the number of deaths caused by myocardial infarction over the course of that year. The mortality rate of sepsis in these studies was estimated to be about 17.9% and 28.6%, respectively. These studies (Refs. 157 and 165), as well as others (Refs. 166, 167, and 168), agree that the risk of sepsis is increased with age (after one year old), male sex, comorbid illness, and in non-whites. The incidence and prevalence of sepsis is widely believed to be increasing (Refs. 157, 165, 166, 167, and 169). While the mortality rate of sepsis has been decreasing slightly with advances in medical care, the overall number of deaths due to sepsis has been increasing (Ref. 157).

Vaccinia

Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, FDA believes that vaccinia virus is potentially transmissible via HCT/Ps. Two different investigators, in 1930 and 1953, reported that vaccinia virus could sometimes be isolated from a patient's blood 3-10 days after vaccination (Ref. 8). These studies did not use the less virulent NYCBOH strain of vaccinia virus that comprises currently available vaccines in the U.S. Using the NYCBOH strain of

vaccinia virus, other investigators were only able to detect virus in the blood of patients with disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination.

A frequent complication of smallpox vaccination is autoinoculation or inadvertent inoculation of a contact (Refs. 170, 171, and 172). Vaccinia virus is readily recovered from the vaccination site until the vaccination scab spontaneously separates from the skin. The scabs themselves contain infectious virus. Thus, although viremia is unlikely once an immune response is initiated, recipients of the vaccine could still inadvertently infect contacts that touch the vaccination site or dressing (Ref. 173). Vaccinia virus can be recovered from the skin at the vaccination site for a mean duration of 7.8 days, with a range of 0 to 18 days (Ref. 174). After an individual is vaccinated with the vaccinia virus, vaccinia can be accidentally spread to other parts of the body and to others since the virus is capable of contact transmission (Refs. 11, 172, and 175). Nosocomial spread of vaccinia has also been reported (Ref. 172). Recent literature describes the conjugal transfer of vaccinia from 2 different active-duty military personnel to their respective partners after smallpox vaccination (Ref. 176).

Smallpox vaccination was routinely performed in the U.S. until 1971. In recent years, smallpox vaccination has been recommended only for laboratory personnel working with certain orthopox viruses, including vaccinia and smallpox. On June 20, 2002, the Advisory Committee for Immunization Practices (ACIP) of the CDC recommended that smallpox vaccine also be given to persons pre-designated to conduct investigation and follow-up of initial smallpox cases and to personnel in facilities that are pre-designated to serve as referral centers to provide care for initial smallpox cases. On December 13, 2002, President Bush announced his decision to begin a smallpox vaccination campaign targeted to those military and civilian personnel who have an occupational risk of contracting smallpox. There is a policy in place to vaccinate Department of Defense (DoD) personnel who are deployed to areas designated as high-threat by the Secretary of Defense. In addition, DoD offers voluntary smallpox vaccination for military members and their families, civilian employees and their family members, and contract personnel serving at Department of State missions in Near East Asia, Israel, Turkey, North Africa, Lebanon, Syria, Jordan, Egypt, and Korea (Refs. 177 through 180). Implementation and review of these policies appear to be ongoing (Ref. 181). According to the DoD Smallpox Vaccination Program website (updated 4/14/05) (Ref. 182), more than 760,000 people have been vaccinated with smallpox vaccine since December 2002 through its vaccination program. Since the smallpox vaccination program affects a large number of people throughout the country, we believe the incidence of vaccinia in the donor population is sufficient to warrant its addition to the list of relevant communicable diseases.

EXHIBIT 7

Wyeth®

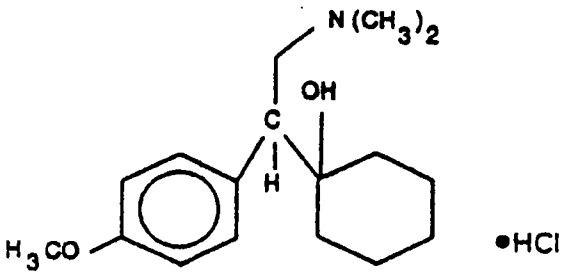
Effexor® XR

(venlafaxine hydrochloride)
Extended-Release Capsules

℞ only

DESCRIPTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is

hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

Absorption

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

Administration of Effexor XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets (C_{max}'s for immediate release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; T_{max}'s were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Effexor XR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Effexor XR capsule.

Metabolism and Excretion

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations

Age and Gender: A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see **DOSAGE AND ADMINISTRATION**).

Extensive/Poor Metabolizers: Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Renal Disease: In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10 to 70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR=10 to 70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Clinical Trials

Major Depressive Disorder

The efficacy of Effexor XR (venlafaxine hydrochloride) extended-release capsules as a treatment for major depressive disorder was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depressive disorder.

A 12-week study utilizing Effexor XR doses in a range 75 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing Effexor XR doses in a range 75 to 225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of Effexor XR over placebo on the HAM-D total score, HAM-D Depressed Mood Item, the MADRS total score, the Clinical Global Impressions (CGI) Severity of Illness item, and the CGI Global Improvement item. In both studies, Effexor XR was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

A 4-week study of inpatients meeting DSM-III-R criteria for major depressive disorder with melancholia utilizing Effexor (the immediate release form of venlafaxine) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of Effexor over placebo. The mean dose in completers was 350 mg/day.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

In one longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR (75, 150, or 225 mg, qAM) were randomized to continuation of their same Effexor XR dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity of Illness item score of ≤3 and a HAM-D-21 total score of ≤10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥4 (moderately ill), (2) 2 consecutive CGI Severity of Illness item scores of ≥4, or (3) a final CGI Severity of Illness item score of ≥4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥20; (2) no more than 2 HAM-D-21 total scores >10, and (3) no single CGI Severity of Illness item score ≥4(moderately ill)] during an initial 26 weeks of treatment on Effexor (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥4, was for up to 52 weeks. Patients receiving continued Effexor treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

Generalized Anxiety Disorder

The efficacy of Effexor XR capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies, one 6-month, placebo-controlled, fixed-dose study, and one 6-month, placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.

One 8-week study evaluating Effexor XR doses of 75, 150, and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the Clinical Global Impressions (CGI) scale. While there was also evidence for superiority over placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose. A second 8-week study evaluating Effexor XR doses of 75 and 150 mg/day and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. A dose-response relationship for effectiveness in GAD was not clearly established in the 75 to 225 mg/day dose range utilized in these two studies.

Two 6-month studies, one evaluating Effexor XR doses of 37.5, 75, and 150 mg/day and the other evaluating Effexor XR doses of 75 to 225 mg/day, showed that daily doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale during 6 months of treatment. While there was also evidence for superiority over placebo for the 37.5 mg/day dose, this dose was not as consistently effective as the higher doses.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

Social Anxiety Disorder (Social Phobia)

The efficacy of Effexor XR capsules as a treatment for Social Anxiety Disorder (also known as Social Phobia) was established in two double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75 to 225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Effexor XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder

Effexor XR (venlafaxine hydrochloride) extended-release capsules is indicated for the treatment of major depressive disorder.

The efficacy of Effexor XR in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see **Clinical Trials**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two-week period: depressed mood,

markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Effexor (the immediate release form of venlafaxine) in the treatment of major depressive disorder in inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see **Clinical Trials**). The safety and efficacy of Effexor XR in hospitalized depressed patients have not been adequately studied.

The efficacy of Effexor XR in maintaining a response in major depressive disorder for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see **Clinical Trials**). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Generalized Anxiety Disorder

Effexor XR is indicated for the treatment of Generalized Anxiety Disorder (GAD) as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of Effexor XR in the treatment of GAD was established in 8-week and 6-month placebo-controlled trials in outpatients diagnosed with GAD according to DSM-IV criteria (see **Clinical Trials**).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

Although the effectiveness of Effexor XR has been demonstrated in 6-month clinical trials in patients with GAD, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Social Anxiety Disorder

Effexor XR is indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia, as defined in DSM-IV (300.23).

Social Anxiety Disorder (DSM-IV) is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared

situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Effexor XR in the treatment of Social Anxiety Disorder was established in two 12-week placebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV). Effexor XR has not been studied in children or adolescents with Social Anxiety Disorder (see **Clinical Trials**).

The effectiveness of Effexor XR in the long-term treatment of Social Anxiety Disorder, ie, for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended-release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

Sustained Hypertension

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. Among patients treated with 75 to 375 mg/day of Effexor XR in premarketing studies in patients with major depressive disorder, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5 to 225 mg/day of Effexor XR in premarketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Among patients treated with 75 to 225 mg/day of Effexor XR in premarketing Social Anxiety Disorder studies, 1.4% (4/277) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3% to 7% at 100 to 300 mg/day to 13% at doses above 300 mg/day. An insufficient number of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled premarketing studies in patients with major depressive disorder with Effexor XR 75 to 225 mg/day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled premarketing GAD studies with Effexor XR 37.5 to 225 mg/day, up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In placebo-controlled premarketing Social Anxiety Disorder studies with Effexor XR 75 to 225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 1.6 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.1 mm Hg for placebo-treated patients.

In premarketing major depressive disorder studies, 0.7% (5/705) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In premarketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 12 weeks, 0.4% (1/277) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In this patient, the blood pressure increase was modest (13 mm Hg, SDBP).

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

General

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Effexor XR (venlafaxine hydrochloride) extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder, GAD, and Social Anxiety Disorder studies, as shown in Table 1.

Table 1
Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, and Social Anxiety Disorder Trials

	Major Depressive Disorder		GAD		Social Anxiety Disorder	
Symptom	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274
Insomnia	17%	11%	15%	10%	23%	7%
Nervousness	10%	5%	6%	4%	11%	3%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in major depressive disorder studies.

In GAD trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of the patients treated with Effexor XR up to 8 weeks and 2% and 0.7%, respectively, of the patients treated with Effexor XR up to 6 months.

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 3% and 0%, respectively, of the patients treated with Effexor XR up to 12 weeks.

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (4%) in the pool of short-term studies in major depressive disorder. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of Effexor XR treatment. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled major depressive disorder trials. Discontinuation rates for anorexia and weight loss associated with Effexor XR were low (1.0% and 0.1%, respectively, of Effexor XR-treated patients in major depressive disorder studies).

In the pool of GAD studies, treatment-emergent anorexia was reported in 8% and 2% of patients receiving Effexor XR and placebo up to 8 weeks, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 1% of the placebo-treated patients up to 6 months in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 8 weeks (0.9% and 0.3%, respectively).

In the pool of Social Anxiety Disorder studies, treatment-emergent anorexia was reported in 20% and 2% of patients receiving Effexor XR and placebo up to 12 weeks, respectively. A loss of 7% or more of body weight occurred in none of the Effexor XR-treated or the placebo-treated patients up to 12 weeks in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 12 weeks (0.4% and 0.0%, respectively).

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products.

Activation of Mania/Hypomania

During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of Effexor XR-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Effexor XR-treated patients and 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, no Effexor XR-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with Effexor, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs to treat major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Effexor XR should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Seizures

During premarketing experience, no seizures occurred among 705 Effexor XR-treated patients in the major depressive disorder studies, among 1381 Effexor XR-treated patients in GAD studies, or among 277 Effexor XR-treated patients in Social Anxiety Disorder studies. In all premarketing major depressive disorder trials with Effexor, seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Effexor XR, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation
Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see **ADVERSE REACTIONS-Laboratory Changes**). Measurement of serum cholesterol levels should be considered during long-term treatment.

Suicide
The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

The same precautions observed when treating patients with major depressive disorder should be observed when treating patients with GAD or Social Anxiety Disorder.

Use in Patients With Concomitant Illness
Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor XR to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. The electrocardiograms were analyzed for 275 patients who received Effexor XR and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in major depressive disorder, for 610 patients who received Effexor XR and 298 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD, and for 195 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QTc for Effexor XR-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 2.8 msec for Effexor XR and decrease of 2.0 msec for placebo).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and no change for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo).

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, Effexor-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (eg, patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

Evaluation of the electrocardiograms for 769 patients who received immediate release Effexor in 4- to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR = 10 to 70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see **DOSAGE AND ADMINISTRATION**). Effexor XR, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Effexor XR (venlafaxine hydrochloride) extended-release capsules:

Interference with Cognitive and Motor Performance

Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine therapy does not adversely affect their ability to engage in such activities.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations, since there is a potential for interactions.

Alcohol

Although venlafaxine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking venlafaxine.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing
Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Alcohol
A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine
Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam
Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

Haloperidol
Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Lithium
The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV

also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also *CNS-Active Drugs*, below).

Drugs Highly Bound to Plasma Proteins

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor XR to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Inhibit Cytochrome P450 Isoenzymes

CYP2D6 Inhibitors: In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers (see *Metabolism and Excretion* under **CLINICAL PHARMACOLOGY**). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied.

Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes

CYP2D6: In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine - Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone - Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4: Venlafaxine did not inhibit CYP3A4 in vitro. This finding was confirmed in vivo by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir - In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 in vitro. This finding was confirmed in vivo by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9: Venlafaxine did not inhibit CYP2C9 in vitro. The clinical significance of this finding is unknown.

CYP2C19: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above).

Monoamine Oxidase Inhibitors
See **CONTRAINDICATIONS** and **WARNINGS.**

CNS-Active Drugs
Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

Electroconvulsive Therapy
There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment.

Postmarketing Spontaneous Drug Interaction Reports
See **ADVERSE REACTIONS, Postmarketing Reports.**

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the in vitro BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the in vivo chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the in vitro Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

Labor and Delivery

The effect of venlafaxine on labor and delivery in humans is unknown.

Nursing Mothers

Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

In pediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm.

Geriatric Use

Approximately 4% (14/357), 6% (77/1381), and 2% (6/277) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see **CLINICAL PHARMACOLOGY**). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information included in the **Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR** subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Effexor XR®, and on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder. Information on additional adverse events associated with Effexor XR in the entire development program for the formulation and with Effexor (the immediate release formulation of venlafaxine) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR

Adverse Events Associated with Discontinuation of Treatment

Approximately 11% of the 357 patients who received Effexor® XR (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for either indication) are shown in Table 2.

Table 2
Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

Adverse Event	Percentage of Patients Discontinuing Due to Adverse Event					
	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274
Body as a Whole						
Asthenia	--	--	3%	<1%	1%	<1%
Headache	--	--	--	--	2%	<1%
Digestive System						
Nausea	4%	<1%	8%	<1%	4%	0%
Anorexia	1%	<1%	--	--	--	--
Dry Mouth	1%	0%	2%	<1%	--	--
Vomiting	--	--	1%	<1%	--	--
Nervous System						
Dizziness	2%	1%	--	--	2%	0%
Insomnia	1%	<1%	3%	<1%	3%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%
Nervousness	--	--	2%	<1%	--	--
Tremor	--	--	1%	0%	--	--
Anxiety	--	--	--	--	1%	<1%
Skin						
Sweating	--	--	2%	<1%	1%	0%
Urogenital System						
Impotence[5]	--	--	--	--	3%	0%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the GAD studies were fixed dose and one was flexible dose. Both of the Social Anxiety Disorder studies were flexible dose.

[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 192], % Placebo [n = 202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

[3] In two short-term U.S. placebo-controlled trials for GAD, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 476]), % Placebo [n = 201]: headache (4%, <1%); vasodilatation (1%, 0%); anorexia (2%, <1%); dizziness (4%, 1%); thinking abnormal (1%, 0%); and abnormal vision (1%, 0%).

[4] In long-term placebo-controlled trials for GAD, the following was also a common event leading to discontinuation and was considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 535], % Placebo [n = 257]): decreased libido (1%, 0%).

[5] Incidence is based on the number of men (Effexor XR = 158, placebo = 153).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

Tables 3, 4, and 5 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day), of GAD (up to 8 weeks; dose range of 37.5 to 225 mg/day), and of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), respectively, in 2% or more of patients treated with Effexor XR (venlafaxine hydrochloride) where the incidence in patients treated with Effexor XR was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Commonly Observed Adverse Events from Tables 3, 4, and 5:

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder (Table 3): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Generalized Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication (Table 4): Abnormalities of sexual function (abnormal ejaculation and impotence), gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating.

Social Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the Social Anxiety Disorder indication (Table 5): Asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

Table 3
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System	**Effexor XR**	**Placebo**
Preferred Term	(n = 357)	(n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%

Body System Preferred Term	% Reporting Event Effexor XR (n = 357)	 Placebo (n = 285)
Special Senses		
Abnormal Vision[5]	4%	<1%
Urogenital System		
Abnormal Ejaculation (male)[6,7]	16%	<1%
Impotence[7]	4%	<1%
Anorgasmia (female)[8,9]	3%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Mostly "delayed ejaculation."
[7] Incidence is based on the number of male patients.
[8] Mostly "delayed orgasm" or "anorgasmia."
[9] Incidence is based on the number of female patients.

Table 4
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams[4]	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	3%	<1%
Skin		
Sweating	10%	3%
Special Senses		
Abnormal Vision[5]	5%	<1%
Urogenital System		
Abnormal Ejaculation[6,7]	11%	<1%
Impotence[7]	5%	<1%
Orgasmic Dysfunction (female)[8,9]	2%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.

[2] <1% means greater than zero but less than 1%.

[3] Mostly "hot flashes."

[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."

[5] Mostly "blurred vision" and "difficulty focusing eyes."

[6] Includes "delayed ejaculation" and "anorgasmia."

[7] Percentage based on the number of males (Effexor XR = 525, placebo = 220).

[8] Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."

[9] Percentage based on the number of females (Effexor XR = 856, placebo = 335).

Table 5
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 277)	**Placebo** (n = 274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu Syndrome	6%	5%
Accidental Injury	5%	3%
Abdominal Pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation[3]	3%	1%
Palpitation	3%	1%
Digestive System		
Nausea	29%	9%
Anorexia[4]	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0%
Metabolic/Nutritional		
Weight Loss	4%	0%
Nervous System		
Insomnia	23%	7%
Dry Mouth	17%	4%
Dizziness	16%	8%
Somnolence	16%	8%
Nervousness	11%	3%
Libido Decreased	9%	<1%
Anxiety	5%	3%
Agitation	4%	1%
Tremor	4%	<1%
Abnormal Dreams[5]	4%	<1%
Paresthesia	3%	<1%
Twitching	2%	0%
Respiratory System		
Yawn	5%	<1%
Sinusitis	2%	1%
Skin		
Sweating	13%	2%

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Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Special Senses		
Abnormal Vision[6]	6%	3%
Urogenital System		
Abnormal Ejaculation[7,8]	16%	1%
Impotence[8]	10%	1%
Orgasmic Dysfunction[9,10]	8%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: back pain, depression, dysmenorrhea, dyspepsia, infection, myalgia, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "blurred vision."
[7] Includes "delayed ejaculation" and "anorgasmia."
[8] Percentage based on the number of males (Effexor XR = 158, placebo = 153).
[9] Includes "abnormal orgasm" and "anorgasmia."
[10] Percentage based on the number of females (Effexor XR = 119, placebo = 121).

Vital Sign Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with no change for placebo. (See the **Sustained Hypertension** section of **WARNINGS** for effects on blood pressure.)

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL

and 2.3 mg/dL, respectively while placebo subjects experienced mean final decreases of 4.9 mg/dL and 7.7 mg/dL, respectively. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 11.4 mg/dL compared with a mean final decrease of 2.2 mg/dL for placebo.

Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-***Serum Cholesterol Elevation*).

ECG Changes

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**).

Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR

During its premarketing assessment, multiple doses of Effexor XR were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 5356 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 3, 4, and 5 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that,

although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: **frequent** adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients.

Body as a whole - **Frequent:** chest pain substernal, chills, fever, neck pain; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare:** appendicitis, bacteremia, carcinoma, cellulitis.

Cardiovascular system - **Frequent:** migraine, postural hypotension, tachycardia; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor.

Digestive system - **Frequent:** increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare:** cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, proctitis, increased salivation, soft stools, tongue discoloration.

Endocrine system - **Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura.

Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous system - **Frequent:** amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; **Infrequent:** akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor; **Rare:** akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis.

Respiratory system - **Frequent:** cough increased, dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and appendages - **Frequent:** pruritus; **Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital system - **Frequent:** metrorrhagia,* prostatic disorder (prostatitis and enlarged prostate),* urination impaired, vaginitis*; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare:** abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.*

*Based on the number of men and women as appropriate.

Postmarketing Reports

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation,

supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Effexor XR (venlafaxine hydrochloride) extended-release capsules is not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see **DOSAGE AND ADMINISTRATION**).

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Among the patients included in the premarketing evaluation of Effexor XR, there were 2 reports of acute overdosage with Effexor XR in major depressive disorder trials, either alone or in combination with other drugs. One patient took a combination of 6 g of Effexor XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of Effexor XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were 2 reports of acute overdose with Effexor XR in GAD trials. One patient took a combination of 0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Effexor XR. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. These symptoms resolved over the next week.

There were no reports of acute overdose with Effexor XR in Social Anxiety Disorder trials.

Among the patients included in the premarketing evaluation with Effexor, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference®* (*PDR*).

DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

Initial Treatment

Major Depressive Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of Effexor XR in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for Effexor XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140 to 180 mg/day (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for Effexor (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg/day is very limited. (See **PRECAUTIONS-General-***Use in Patients with Concomitant Illness.*)

Generalized Anxiety Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (GAD), the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in GAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**.)

Social Anxiety Disorder (Social Phobia)

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Social Anxiety Disorder, the initial dose of Effexor XR was 75 mg/day and the maximum dose was 225 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in patients with Social Anxiety Disorder was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See the *Use in Patients with Concomitant Illness* section of **PRECAUTIONS**).

Switching Patients from Effexor Tablets

Depressed patients who are currently being treated at a therapeutic dose with Effexor may be switched to Effexor XR at the nearest equivalent dose (mg/day), eg, 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 to 70 mL/min) compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 25% to 50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of major depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment

There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder should be treated with Effexor XR.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Generalized Anxiety Disorder, Effexor XR has been shown to be effective in 6-month clinical trials. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

In patients with Social Anxiety Disorder, there are no efficacy data beyond 12 weeks of treatment with Effexor XR. The need for continuing medication in patients with Social Anxiety Disorder who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR

When discontinuing Effexor XR after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received Effexor XR for 6 weeks or more should have their dose tapered over at least a 2-week period. In clinical trials with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary.

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials of major depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, seizures, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. It is therefore recommended that the dosage of Effexor XR be tapered gradually and the patient monitored. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Discontinuation effects are well known to occur with antidepressants.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Effexor® XR (venlafaxine hydrochloride) extended-release capsules are available as follows:

37.5 mg, grey cap/peach body with **W** and "Effexor XR" on the cap and "37.5" on the body.
NDC 0008-0837-01, bottle of 100 capsules.
NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

Bottles: Protect from light. Dispense in light-resistant container.

Blisters: Protect from light. Use blister carton to protect contents from light.

75 mg, peach cap and body with **W** and "Effexor XR" on the cap and "75" on the body.
NDC 0008-0833-01, bottle of 100 capsules.
NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

150 mg, dark orange cap and body with W and "Effexor XR" on the cap and "150" on the body.
NDC 0008-0836-01, bottle of 100 capsules.
NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

The appearance of these capsules is a trademark of Wyeth Pharmaceuticals.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of May 2007 I electronically filed the foregoing document, **REDACTED VERSION OF DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M., IN SUPPORT OF IMPAX'S RESPONSIVE CLAIM CONSTRUCTION BRIEF,** with the Clerk of the Court using CM/ECF which sent notification of such filing to the following:

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Additionally, I hereby certify that on the same date, the foregoing document was served as indicated below:

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